

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
WO 2006/102535 A2

(51) International Patent Classification:
A61K 31/44 (2006.01)

(21) International Application Number:
PCT/US2006/010640

(22) International Filing Date: 22 March 2006 (22.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/664,139 22 March 2005 (22.03.2005) US

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **SULFONYL CONTAINING COMPOUNDS AS CYSTEINE PROTEASE INHIBITORS**

(57) Abstract: The present invention is directed to compounds that are inhibitors of cysteine proteases, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is directed to pharmaceutical compositions comprising these compounds and processes for preparing them.

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SULFONYL CONTAINING COMPOUNDS AS CYSTEINE PROTEASE INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

- 5 [0001] This application claims the benefit of Provisional Patent Application No. 60/664,139, filed March 22, 2005 the content of which is incorporated herein by reference.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] NOT APPLICABLE

- 10 **REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER
PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.**

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

Field of the Invention

- 15 [0004] The present invention is directed to compounds that are inhibitors of cysteine proteases, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is also directed to pharmaceutical compositions comprising these compounds and processes for preparing them.

State of the Art

- 20 [0005] Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increased expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a
- 25 number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. For example, increased cathepsin B levels and redistribution of the enzyme are found in tumors; thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid

arthritis, osteoarthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

[0006] The prominent expression of cathepsin K in osteoclasts and osteoclast-related multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in osteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest that the enzyme plays a role in pulmonary disorders as well.

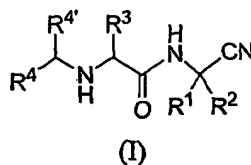
[0007] Cathepsin L is implicated in normal lysosomal proteolysis as well as in several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, neuropathic pain, and Hashimoto's thyroiditis. In addition, cathepsin S is implicated in: allergic disorders, including, but not limited to asthma; and allogeneic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts.

[0008] In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules which inhibit the activity of this class of enzymes, in particular molecules which inhibit cathepsins B, K, L, F, and/or S, will therefore be useful as therapeutic agents.

20

SUMMARY OF THE INVENTION

[0009] In a first aspect, this invention is directed to a compound of Formula (I):



25 wherein:

R¹ is hydrogen, alkyl, or haloalkyl;

R² is hydrogen, alkyl, or haloalkyl; or

R¹ and R² taken together with the carbon atom to which R¹ and R² are attached form cycloalkylene optionally substituted with one to four fluoro, piperidin-4-yl wherein the

nitrogen atom of the piperidiny ring is substituted with alkyl, haloalkyl, or cycloalkyl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1,1-dioxohexahydrothiopyran-4-yl, or -CH₂-O-CH₂-;

R³ is -alkylene-SO₂-alkyl, -alkylene-SO₂-haloalkyl, , -alkylene-SO₂-cycloalkyl, -
 5 alkylene-SO₂-cycloalkylalkyl, -alkylene-SO₂-aryl, -alkylene-SO₂-aralkyl, -alkylene-SO₂-heterocycloalkyl, -alkylene-SO₂-heterocycloalkylalkyl, -alkylene-SO₂-heteroaryl, -alkylene-SO₂-heteroaralkyl, -alkylene-SO₂-haloalkylene-aryl or -alkylene-SO₂-haloalkylene-heteroaryl
 wherein the aromatic or alicyclic ring in R³ is optionally substituted with one, two, or three R^a independently selected from alkyl, alkylsulfonyl, haloalkyl, alkoxy, hydroxy,
 10 hydroxyalkyl, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl, amino, alkylamino, dialkylamino, aminocarbonyl, or acyl and further wherein the aromatic ring in R^a is optionally substituted with one, two, or three R^b independently selected from alkyl, alkoxy, alkylsulfonyl, hydroxy, or halo;

R⁴ is hydrogen, alkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl attached via a
 15 carbon ring atom wherein the aromatic or alicyclic ring in R⁴ is optionally substituted by one, two, or three R^f independently selected from alkyl, halo, hydroxy, alkoxy, alkylcarbonyl, alkylsulfonyl, alkylsulfonylamino, aminocarbonyl, haloalkyl, haloalkoxy, carboxy, or alkoxycarbonyl;

R^{4'} is difluoromethyl, trifluoromethyl, 1,1,2,2,2-pentafluoroethyl,
 20 chlorodifluoromethyl, 1,1-dichloro-2,2,2-trifluoroethyl, 1,1,2,2-tetrafluoroethyl, trichloromethyl, dichlorofluoromethyl, 1,1,2,2,3,3,3-heptafluoropropyl, or 1,1,2,2,3,3,3-hexafluoropropyl, or
 a pharmaceutically acceptable salt thereof provided that:

(a) when R¹ and R² taken together with the carbon atom to which R¹ and R² are
 25 attached form cyclopropylene, R³ is phenylmethanesulfonylmethyl, cyclopropylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, 2-difluoromethoxyphenylmethanesulfonylmethyl, or 2-trifluoromethylpyridin-6-methanesulfonylmethyl, R⁴ is phenyl, 4-hydroxyphenyl, 3-bromophenyl, 4-fluorophenyl, 3-chloro-4-hydroxyphenyl, 3,4-difluorophenyl, or 3,4,5-trifluorophenyl, then R^{4'} is not
 30 trifluoromethyl or difluoromethyl;

(b) when R¹ and R² taken together with the carbon atom to which R¹ and R² are attached form cyclopropylene, R³ is phenylmethanesulfonylmethyl, difluoromethoxyphenylmethanesulfonylmethyl, or cyclopropylmethanesulfonylmethyl, R⁴ is

furan-2-yl, indol-3-yl, thiophen-2-yl, 1-methylpyrrol-2-yl, pyridin-2-yl, thiophen-3-yl or 1-oxo-1-methylpyrrol-2-yl, then R^{4'} is not difluoromethyl or trifluoromethyl;

(c) when R¹ and R² taken together with the carbon atom to which R¹ and R² are attached form 1,1-dioxohexahydrothiopyran-4-ylene, R³ is phenylmethanesulfonylmethyl, 4-fluorophenylmethanesulfonylmethyl, or difluoromethoxyphenylmethanesulfonylmethyl, then R^{4'} is not trifluoromethyl; and

(d) when R¹ and R² taken together with the carbon atom to which R¹ and R² are attached form tetrahydropyran-4-ylene or tetrahydrothiopyran-4-ylene, R³ is cyclopropylmethanesulfonylmethyl or difluoromethoxyphenylmethanesulfonylmethyl, R⁴ is 4-fluorophenyl, then R^{4'} is not trifluoromethyl.

[0010] In a second aspect, this invention is directed to a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

[0011] In a third aspect, this invention is directed to a method for treating a disease in an animal mediated by cysteine proteases, in particular cathepsin S, which method comprises administering to the animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

[0012] In a fourth aspect, this invention is directed to processes for preparing compounds of Formula (I).

[0013] In a fifth aspect, this invention is directed to a method of treating a patient undergoing a therapy wherein the therapy causes an immune response, preferably a deleterious immune response, in the patient comprising administering to the patient a compound of Formula (I) or a pharmaceutically acceptable salt thereof. Preferably, the immune response is mediated by MHC class II molecules. The compound of this invention can be administered prior to, simultaneously, or after the therapy. Preferably, the therapy involves treatment with a biologic. Preferably, the therapy involves treatment with a small molecule.

[0014] Preferably, the biologic is a protein, preferably an antibody, more preferably monoclonal antibody. More preferably, the biologic is Remicade[®], Refacto[®], Referon-A[®], Factor VIII, Factor VII, Betaseron[®], Epogen[®], Enbrel[®], Interferon beta, Botox[®],

Fabrazyme[®], Elspar[®], Cérezyme[®], Myobloc[®], Aldurazyme[®], Verluma[®], Interferon alpha, Humira[®], Aranesp[®], Zevalin[®] or OKT3.

[0015] Preferably, the treatment involves use of heparin, low molecular weight heparin, procainamide or hydralazine.

- 5 [0016] In a sixth aspect, this invention is directed to a method of treating immune response in an animal that is caused by administration of a biologic to the animal which method comprises administering to the animal in need of such treatment a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

- 10 [0017] In a seventh aspect, this invention is directed to a method of conducting a clinical trial for a biologic comprising administering to an individual participating in the clinical trial a compound of Formula (I) or a pharmaceutically acceptable salt thereof with the biologic.

- 15 [0018] In an eighth aspect, this invention is directed to a method of prophylactically treating a patient undergoing treatment with a biologic with a compound of Formula (I) or a pharmaceutically acceptable salt thereof to treat the immune response caused by the biologic in the patient.

[0019] In a ninth aspect, this invention is directed to a method of determining the loss in the efficacy of a biologic in an animal due to the immune response caused by the biologic comprising administering the biologic to the animal in the presence and absence of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

- 20 [0020] In a tenth aspect, this invention is directed to a method of improving efficacy of a biologic in an animal comprising administering the biologic to the animal with a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0021] In an eleventh aspect, this invention is directed to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

- 25 Preferably, the medicament is for use in the treatment of a disease mediated by Cathepsin S.

- [0022] In a twelfth aspect, this invention is directed to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for combination therapy with a biologic, wherein the compound of this invention treats the immune response caused by the biologic. Preferably, the compound(s) of the invention is administered prior to the administration of the biological agent. Preferably, the compound(s)
- 30

of the invention is administered concomitantly with the biological agent. Preferably, the compound(s) of the invention is administered after the administration of the biological agent.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

5 [0023] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

[0024] "Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures e.g., cycloalkyl and heterocycloalkyl rings as defined herein.

10 [0025] "Alkyl" represented by itself means a straight or branched, saturated aliphatic radical containing one to eight carbon atoms, unless otherwise indicated e.g., alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, and the like.

[0026] "Alkylene", unless indicated otherwise, means a straight or branched, saturated aliphatic, divalent radical having the number of one to six carbon atoms, e.g., methylene
15 (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-) 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene (-CH₂CH₂CH₂CH₂CH₂-), and the like.

[0027] "Alkoxy" refers to a -OR radical where R is an alkyl group as defined above e.g., methoxy, ethoxy, and the like.

20 [0028] "Alkylsulfonyl" refers to a -SO₂R radical where R is an alkyl group as defined above e.g., methylsulfonyl, ethylsulfonyl, and the like.

[0029] "Alkylsulfonylamino" refers to a -NHSO₂R radical where R is an alkyl group as defined above e.g., methylsulfonylamino, ethylsulfonylamino, and the like.

[0030] "Alkoxycarbonyl" refers to a -C(O)OR radical where R is an alkyl group as defined
25 above e.g., methoxycarbonyl, ethoxycarbonyl, and the like.

[0031] "Amino" means -NH₂ radical.

[0032] "Aminocarbonyl" refers to a -CONRR' radical where R and R' are independently hydrogen or alkyl, e.g., -CONH₂, methylaminocarbonyl, dimethylaminocarbonyl, and the like.

[0033] "Alkylamino" or "dialkylamino" refers to a -NHR and -NRR' radical respectively, where R and R' are independently alkyl group as defined above e.g., methylamino, dimethylamino, and the like.

5 [0034] "Acyl" means a -COR radical where R is alkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl as defined herein e.g., acetyl, trifluoroacetyl, and the like. When R is alkyl it is referred to herein as alkylcarbonyl.

[0035] "Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

10 [0036] "Aromatic" refers to a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi electrons is equal to $4n+2$.

[0037] "Aryl" refers to a monocyclic or fused bicyclic ring assembly containing 6 to 10 ring carbon atoms wherein each ring is aromatic e.g., phenyl or naphthyl.

15 [0038] "Aralkyl" refers to a -(alkylene)-aryl radical where alkylene and aryl are as defined above, e.g., benzyl, 2-phenylethyl, and the like.

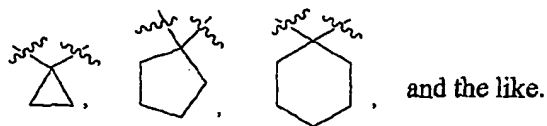
[0039] "Biologic" means a therapeutic agent originally derived from living organisms for the treatment or management of a disease. Examples include, but are not limited to, proteins (recombinant and plasma derived), monoclonal or polyclonal, humanized or murine antibodies, toxins, hormones, and the like. Biologics are currently available for the treatment
20 of a variety of diseases such as cancer, rheumatoid arthritis, and hemophilia.

[0040] "Carboxy" refers to -C(O)OH radical.

[0041] "Cycloalkyl" refers to a monovalent saturated monocyclic ring containing three to eight ring carbon atoms e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

25 [0042] "Cycloalkylalkyl" refers to a -(alkylene)-R radical where R is cycloalkyl as defined above e.g., cyclopropylmethyl, cyclobutylethyl, cyclobutylmethyl, and the like

[0043] "Cycloalkylene" refers to a divalent saturated monocyclic ring containing three to eight ring carbon atoms. For example, the instance wherein "R¹ and R² together with the carbon atom to which both R¹ and R² are attached form cycloalkylene" includes, but is not limited to, the following:



[0044] "Derived" means a similar agent can be traced to.

5 [0045] "Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

[0046] "Deleterious immune response" means an immune response that prevents effective treatment of a patient or causes disease in a patient. As an example, dosing a patient with a murine antibody either as a therapy or a diagnostic agent causes the production of human antmouse antibodies that prevent or interfere with subsequent treatments. The incidence of antibody formation versus pure murine monoclonals can exceed 70%. (see Khazaeli, M. B. *et al. J. Immunother.* 1994, 15, pp 42-52; Dillman R. O. *et al. Cancer Biother.* 1994, 9, pp 17-28; and Reinsberg, J. *Hybridoma.* 1995, 14, pp 205-208). Additional examples of known agents that suffer from deleterious immune responses are blood-clotting factors such as factor VIII. When administered to hemophilia A patients, factor VIII restores the ability of the blood to clot. Although factor VIII is a human protein, it still elicits an immune response in hemophiliacs as endogenous factor VIII is not present in their blood and thus it appears as a foreign antigen to the immune system. Approximately 29-33% of new patients will produce antibodies that bind and neutralize the therapeutically administered factor VIII (see Lusher J. M. *Semin Thromb Hemost.* 2002, 28(3), pp 273-276). These neutralizing antibodies require the administration of larger amounts of factor VIII in order to maintain normal blood clotting parameters; an expensive regimen of treatment in order to induce immune tolerance (see Briet E *et al. Adv. Exp. Med. Bio.* 2001, 489, pp 89-97). Another immunogenic example is adenoviral vectors. Retroviral therapy remains experimental and is of limited utility. One reason is that the application of a therapeutic virus generates an immune response capable of blocking any subsequent administration of the same or similar virus (see Yiping Yang *et al. J. of Virology.* 1995, 69, pp 2004-2015). This ensures that retroviral therapies must be based on the transient expression of a protein or the direct incorporation of viral sequence into the host genome. Directed research has identified multiple viral neutralizing epitopes recognized by host antibodies (see Hanne, Gahery-Segard *et al. J. of Virology* 1998, 72, pp 2388-2397)

suggesting that viral modifications will not be sufficient to overcome this obstacle. This invention will enable a process whereby an adenoviral therapy will have utility for repeated application. Another example of an immunogenic agent that elicits neutralizing antibodies is the well-known cosmetic agent Botox. Botulin toxin protein, is purified from the

5 fermentation of *Clostridium botulinum*. As a therapeutic agent, it is used for muscle disorders such as cervical dystonia in addition to cosmetic application. After repeated exposure patients generate neutralizing antibodies to the toxin that results in reduced efficacy (see Birklein F. *et al. Ann Neurol.* 2002, 52, pp 68-73 and Rollnik, J. D. *et al. Neurol. Clin. Neurophysiol.* 2001, 2001(3), pp 2-4). A “deleterious immune response” also encompasses

10 diseases caused by therapeutic agents. A specific example of this is the immune response to therapy with recombinant human erythropoietin (EPO). Erythropoietin is used to stimulate the growth of red cells and restore red blood cell counts in patients who have undergone chemotherapy or dialysis. A small percentage of patients develop antibodies to EPO and subsequently are unresponsive to both therapeutically administered EPO and their own

15 endogenous EPO (see Casadevall, N. *et al., NEJM.* 2002, 346, pp 469-475). They contract a disorder, pure red cell aplasia, in which red blood cell production is severely diminished (see Gershon S. K. *et al. NEJM.* 2002, 346, pp 1584-1586). This complication of EPO therapy is lethal if untreated. Another specific example is the murine antibody, OKT3 (a.k.a., Orthoclone) a monoclonal antibody directed towards CD-3 domain of activated T-cells. In

20 clinical trials 20-40% of patients administered OKT3 produce antibodies versus the therapy. These antibodies, besides neutralizing the therapy, also stimulate a strong host immune reaction. The immune reaction is severe enough that patients with high titers of human anti-mouse antibodies are specifically restricted from taking the drug (see Orthoclone package label). A final example is a human antibody therapeutic. Humira® is a monoclonal antibody

25 directed against TNF and is used to treat rheumatoid arthritis patients. When taken alone ~12% of patients develop neutralizing antibodies. In addition, a small percentage of patients given the drug also contract a systemic lupus erythematosus-like condition that is an IgG-mediated immune response induced by the therapeutic agent (see Humira package label).

[0047] Another example of “deleterious immune response” is a host reaction to small

30 molecule drugs. It is known to those skilled in the art that certain chemical structures will conjugate with host proteins to stimulate immune recognition (see Ju. C. *et al.* 2002. *Current Drug Metabolism* 3, pp 367-377 and Kimber I. *et al.* 2002, *Toxicologic Pathology* 30, pp 54-58.) A substantial portion of these host reactions are IgG mediated. Specific “deleterious

immune responses" that are IgG mediated include: hemolytic anemia, Steven-Johnson syndrome and drug induced Lupus.

[0048] "Halo" refers to fluoro, chloro, bromo or iodo.

5 [0049] "Haloalkyl" refers to alkyl as defined above substituted by one or more, preferably one to seven, "halo" atoms, as such terms are defined in this Application. Haloalkyl includes monohaloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like e.g. chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

10 [0050] "Haloalkylene" means alkylene radical as defined above wherein one to four, preferably one or two hydrogen atoms in the alkylene chain has(have) been replaced by fluorine atom(s).

[0051] "Haloalkoxy" refers to a -OR radical where R is haloalkyl group as defined above e.g., trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, and the like.

15 [0052] "Heteroaryl" as a group or part of a group denotes an aromatic monocyclic, bicyclic, or multicyclic moiety of 5 to 10 ring atoms in which one or more, preferably one, two, or three, of the ring atom(s) is(are) selected from nitrogen, oxygen or sulfur, the remaining ring atoms being carbon. Representative heteroaryl rings include, but are not limited to, pyrrolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, 20 quinoliny, isoquinoliny, quinazolinyl, quinoxaliny, pyrazolyl, and the like.

[0053] "Heteroalkyl" refers to a -(alkylene)-heteroaryl radical where alkylene and heteroaryl are as defined above, e.g., pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, and the like.

25 [0054] "Heterocycloalkyl" refers to a saturated or partially unsaturated, monocyclic or bicyclic moiety of 4, 5 or 6 carbon ring atoms wherein one or more, preferably one, two, or three of the carbon ring atoms are replaced by a heteroatom selected from -N=, -N-, -O-, -S-, -SO-, or -S(O)₂- and further wherein one or two ring atoms are optionally replaced by a keto (-CO-) group. The heterocycloalkyl ring is optionally fused to cycloalkyl, aryl or heteroaryl ring as defined herein. Representative examples include, but are not limited to, 4-oxo-5-aza-30 benzospiro[2.4]hept-5-yl, imidazolidinyl, morpholinyl, thiomorpholinyl, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, tetrahydrofuranyl, tetrahydropyranyl,

tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyranyl, 1,1-dioxotetrathiopyranyl, indolinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, and the like.

[0055] "Heterocycloalkylalkyl" refers to a -(alkylene)-R radical where R is heterocycloalkyl as defined above e.g., pyrrolidinylmethyl, tetrahydrofuranylethyl, pyridinylmethyl, and the like.

[0056] "Hydroxy" means -OH radical. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like.

[0057] "Hydroxyalkyl" refers to alkyl as defined above substituted by one or more, preferably one to three hydroxyl groups e.g., hydroxymethyl, hydroxyethyl, and the like.

[0058] "Isomers" mean compounds of Formula (I) having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center that has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula (I) are meant to be encompassed all possible stereoisomers.

[0059] "Optional" or "optionally" or "may be" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the

event or circumstance occurs and instances in which it does not. For example, the phrase "wherein the aromatic ring in R^a is optionally substituted with one or two substituents independently selected from alkyl" means that the aromatic ring may or may not be substituted with alkyl in order to fall within the scope of the invention.

- 5 [0060] The present invention also includes *N*-oxide derivatives of a compound of Formula (I). *N*-oxide derivative mean a compound of Formula (I) in which a nitrogen atom is in an oxidized state (i.e., N→O) e.g., pyridine *N*-oxide, and which possess the desired pharmacological activity.

- [0061] "Pathology" of a disease means the essential nature, causes and development of the
10 disease as well as the structural and functional changes that result from the disease processes.

[0062] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

- 15 [0063] "Pharmaceutically acceptable salts" means salts of compounds of Formula (I) which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic
20 acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methylsulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxy-ethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid,
25 *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

- 30 [0064] Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium

hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

[0065] The present invention also includes prodrugs of a compound of Formula (I).

- 5 Prodrug means a compound that is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of Formula (I). For example an ester of a compound of Formula (I) containing a hydroxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Alternatively an ester of a compound of Formula (I) containing a carboxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of
- 10 compounds of Formula (I) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-*b*-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methylsulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinate. Suitable esters of compounds of Formula (I) containing
- 15 a carboxy group, are for example those described by Leinweber, F.J. *Drug Metab. Res.*, **1987**, *18*, page 379. An especially useful class of esters of compounds of Formula (I) containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard *et al.*, *J. Med. Chem.*, **1989**, *32*, pp 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl
- 20 groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholinomethyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

- [0066] "Protected derivatives" means derivatives of compounds of Formula (I) in which a
- 25 reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula (I) are useful in the preparation of compounds of Formula (I) or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

- 30 [0067] "Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

[0068] "Treatment" or "treating" means any administration of a compound of the present invention and includes:

- (1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,
- (2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or
- (3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

[0069] "Treatment" or "treating" with respect to combination therapy i.e., use with a biologic means any administration of a compound of the present invention and includes:

- (1) preventing the immune response from occurring in an animal which may be predisposed to the immune response but does not yet experience or display the pathology or symptomatology of the immune response,
- (2) inhibiting the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., arresting further development of the pathology and/or symptomatology), or
- (3) ameliorating the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., reducing in degree or severity, or extent or duration, the overt manifestations of the immune response or reversing the pathology and/or symptomatology e.g., reduced binding and presentation of antigenic peptides by MHC class II molecules, reduced activation of T-cells and B-cells, reduced humoral and cell-mediated responses and, as appropriate to the particular immune response, reduced inflammation, congestion, pain, necrosis, reduced loss in the efficacy of a biologic agent, and the like).

[0070] The expression ".....wherein the aromatic or alicyclic ring in R^3 is optionally substituted with one, two, or three R^a independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, amino, alkylamino, dialkylamino, or acyl....." includes instances where the aromatic or alicyclic ring is directly linked to R^3 or where the aromatic or alicyclic ring is part of a group that is directly linked to R^3 e.g. the alicyclic and aromatic ring in -alkylene-SO₂-cycloalkylalkyl, -alkylene-

SO₂-aralkyl, -alkylene-SO₂-heterocycloalkylalkyl, -alkylene-SO₂-heteroaralkyl, or -alkylene-SO₂-haloalkylene-heteroaryl groups that are attached to R³ may or may not be substituted with R^a group(s).

PREFERRED EMBODIMENTS

5 [0071] I. Certain compounds of Formula (I) within the broadest scope set forth in the Summary of the Invention are preferred. For example:

[0072] A. One preferred group of compounds is that wherein R¹ and R² are hydrogen.

[0073] B. Another preferred group of compounds is that wherein R¹ and R² together with the carbon atom to which they are attached form cycloalkylene, preferably R¹ and R² together
10 with the carbon atom to which they are attached form cyclopropylene.

[0074] C. Another preferred group of compounds is that wherein R¹ and R² together with the carbon atom to which they are attached form tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-dioxohexahydrothiopyran-4-yl.

[0075] (a) Within the above preferred groups A, B, and C and the more preferred groups
15 contained therein, a more preferred group of compounds is that wherein:

R³ is -alkylene-SO₂-heteroaralkyl, preferably the heteroaryl ring in the heteroaralkyl moiety is pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinolinyl, or isoquinolinyl and wherein the heteroaryl ring is optionally substituted with one, two, or three R^a independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro,
20 cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, amino, alkylamino, dialkylamino, or acyl and further wherein the aromatic ring in R^a is optionally substituted with one, two, or three R^b independently selected from alkyl, alkoxy, hydroxyl, or halo. Preferably, R³ is 4-CF₃-pyridin-3-ylmethane-sulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, pyridazin-3-ylmethanesulfonylmethyl, 2-CF₃-furan-5-ylmethanesulfonylmethyl, pyrimidin-5-ylmethanesulfonylmethyl, 2-CH₃-thiazol-4-ylmethanesulfonylmethyl, or pyridin-4-ylmethane-sulfonylmethyl.
25

(b) Within the above preferred groups A, B, and C and the more preferred groups contained therein, another even more preferred group of compounds is that wherein:

R³ is -alkylene-SO₂-CF₂-heteroaryl, preferably preferably the heteroaryl ring in the
30 heteroaralkyl moiety is pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinolinyl, or isoquinolinyl and wherein the heteroaryl ring is optionally substituted with one, two, or three

R^a independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxy carbonyl, aryl, heteroaryl, amino, alkylamino, dialkylamino, or acyl and further wherein the aromatic ring in R^a is optionally substituted with one, two, or three R^b independently selected from alkyl, alkoxy, hydroxyl, or halo. Preferably, R³ is 4-CF₃-
 5 pyridin-3-yl-CF₂SO₂-methyl, pyridin-3-yl-CF₂SO₂-methyl, pyridazin-3-yl-CF₂SO₂-methyl, pyrimidin-5-yl-CF₂SO₂-methyl, or pyridin-4-yl-CF₂SO₂-methyl.

[0076] Within the above preferred groups A, A(a-b), B, B(a-b), C, and C(a-b) and the more preferred groups contained therein, a particularly preferred group of compounds is that wherein:

- 10 R⁴ is phenyl optionally substituted with one or two fluoro. Preferably, R⁴ is 4-fluorophenyl, 2,4-difluorophenyl, or 3,4-difluorophenyl;
 and the stereochemistry at the carbon to which R³ is attached is (*R*) and to which R⁴ is attached is (*S*).

[0077] (D) Another preferred group of compounds is that wherein:

- 15 R¹ and R² form cyclopropylene;
 R³ is 4-CF₃-pyridin-3-ylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, pyridazin-3-ylmethanesulfonylmethyl, 2-CF₃-furan-5-ylmethanesulfonylmethyl, pyrimidin-5-ylmethanesulfonylmethyl, 2-CH₃-thiazol-4-ylmethanesulfonylmethyl, pyridin-4-ylmethane-sulfonylmethyl, pyrimidin-4-ylmethanesulfonylmethyl, 2-(1-oxopyrrol-1-yl)ethanesulfonyl-methyl,
 20 cyclopropylmethanesulfonylmethyl, 3,3,3-trifluoropropane-1-sulfonylmethyl, 2-CF₃-pyridin-5-ylmethanesulfonylmethyl, 4-[1.2.4]-triazol-1-ylphenylmethanesulfonylmethyl, 2-(2-oxo-2,3-dihydrobenzimidazol-1-yl)-ethanesulfonylmethyl, 5-oxopyrrolidin-2-ylmethane-sulfonylmethyl, 2-F-pyridin-3-ylmethanesulfonylmethyl, 3-CH₃-oxetan-3-ylmethanesulfonyl-
 25 methyl, 2-phenylethanesulfonylmethyl, fluoro-pyridin-2-ylmethanesulfonylmethyl, fluoro-pyrazin-2-ylmethanesulfonylmethyl, difluoro-pyridin-2-ylmethanesulfonylmethyl, difluoro-pyridin-3-ylmethanesulfonylmethyl, quinolin-2-ylmethanesulfonylmethyl, benzo[1.2.5]thiadiazol-4-ylmethanesulfonylmethyl, benzothiazol-2-ylmethanesulfonylmethyl, 5-methylisoxazol-3-ylmethanesulfonylmethyl, 2-methylpropyl-sulfonylmethyl, 2,6-difluorophenylmethanesulfonylmethyl, 2,4-difluorophenylmethane-sulfonylmethyl, quinolin-3-ylmethanesulfonylmethyl, 4,4,4-trifluorobutyl-1-sulfonylmethyl,
 30 2-CF₃-phenylmethanesulfonylmethyl, 2-CF₃O-phenylmethanesulfonylmethyl, 2-pyridin-2-ylethanesulfonylmethyl, 2-pyridin-3-ylethanesulfonylmethyl, quinolin-8-ylmethane-

sulfonylmethyl, 5-methyl-3-phenylisoxazol-4-ylmethanesulfonylmethyl, 4-methyl-2-phenyl-[1.2.3]triazol-5-ylmethanesulfonylmethyl, 2-cyanophenylmethanesulfonylmethyl, 3-methoxycarbonylphenylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, 1-oxopyridin-2-ylmethanesulfonylmethyl, 1-oxopyridin-3-ylmethanesulfonylmethyl, 5 quinoxalin-2-ylmethanesulfonylmethyl, tetrahydropyran-2*RS*-ylmethanesulfonylmethyl, 2,6-dichloro-phenylmethanesulfonylmethyl, 3-methoxycarbonyl-furan-2-yl-methanesulfonylmethyl, 5-methylisoxazol-3-ylmethanesulfonylmethyl, 2,2-dimethylpropylsulfonylmethyl, ethanesulfonylmethyl, methanesulfonylmethyl, propane-1-sulfonylmethyl, 1*H*-indol-2-ylmethanesulfonylmethyl, 2-(1*H*-indol-3-yl)ethanesulfonylmethyl, 2,2,2-trifluoroethanesulfonylmethyl, benzisoxazol-3-ylmethanesulfonylmethyl, 2-tert-butyl-[1.3.4]thiadiazol-5-ylmethanesulfonylmethyl, 2,4,6-trifluorophenylmethanesulfonylmethyl, 2-pyridin-2-ylethanesulfonylmethyl, 1-ethyl-2,5-dioxopyrrolidin-3-ylmethanesulfonylmethyl or benzisoxazol-3-ylmethanesulfonylmethyl; 10

R^4 is 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, or 3,5-difluorophenyl, more preferably 2,4-difluorophenyl; 15

R^4 is difluoromethyl, trifluoromethyl, or 1,1,2,2,2-pentafluoroethyl, more preferably trifluoromethyl.

[0078] (D) Another preferred group of compounds is that wherein:

R^1 and R^2 form cyclopropylene; 20

R^3 is 4- CF_3 -pyridin-3-ylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, pyridazin-3-ylmethanesulfonylmethyl, 2- CF_3 -furan-5-ylmethanesulfonylmethyl, pyrimidin-5-ylmethanesulfonylmethyl, 2- CH_3 -thiazol-4-ylmethanesulfonylmethyl, pyridin-4-ylmethanesulfonylmethyl, pyrimidin-4-ylmethanesulfonylmethyl, 2-(1-oxopyrrol-1-yl)ethanesulfonylmethyl, 25 cyclopropylmethanesulfonylmethyl, 3,3,3-trifluoropropane-1-sulfonylmethyl, 2- CF_3 -pyridin-5-ylmethanesulfonylmethyl, 4-[1.2.4]-triazol-1-ylphenylmethanesulfonylmethyl, 2-(2-oxo-2,3-dihydrobenzimidazol-1-yl)-ethanesulfonylmethyl, 5-oxopyrrolidin-2-ylmethanesulfonylmethyl, 2-F-pyridin-3-ylmethanesulfonylmethyl, 3- CH_3 -oxetan-3-ylmethanesulfonylmethyl, 2-phenylethanesulfonylmethyl, fluoro-pyridin-2-ylmethanesulfonylmethyl, fluoro-pyrazin-2-ylmethanesulfonylmethyl, difluoro-pyridin-2-ylmethanesulfonylmethyl, difluoro-pyridin-3-ylmethanesulfonylmethyl, quinolin-2-ylmethanesulfonylmethyl, 30 benzo[1.2.5]thiadiazol-4-ylmethanesulfonylmethyl, benzothiazol-2-ylmethanesulfonylmethyl, 5-methylisoxazol-3-ylmethanesulfonylmethyl, 2-methylpropyl-

sulfonylmethyl, 2,6-difluorophenylmethanesulfonylmethyl, 2,4-difluorophenylmethane-
 sulfonylmethyl, quinolin-3-ylmethanesulfonylmethyl, 4,4,4-trifluorobutyl-1-sulfonylmethyl,
 2-CF₃-phenylmethanesulfonylmethyl, 2-CF₃O-phenylmethanesulfonylmethyl, 2-pyridin-2-
 ylethanesulfonylmethyl, 2-pyridin-3-ylethanesulfonylmethyl, quinolin-8-ylmethane-
 5 sulfonylmethyl, 5-methyl-3-phenylisoxazol-4-ylmethanesulfonylmethyl, 4-methyl-2-phenyl-
 [1.2.3]triazol-5-ylmethanesulfonylmethyl, 2-cyanophenylmethanesulfonylmethyl, 3-
 methoxycarbonylphenylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, 1-
 oxopyridin-2-ylmethanesulfonylmethyl, 1-oxopyridin-3-ylmethanesulfonylmethyl,
 quinoxalin-2-ylmethanesulfonylmethyl, tetrahydropyran-2*RS*-ylmethanesulfonylmethyl, 2,6-
 10 dichloro-phenylmethanesulfonylmethyl, 3-methoxycarbonyl-furan-2-yl-
 methanesulfonylmethyl, 5-methylisoxazol-3-ylmethanesulfonylmethyl, 2,2-
 dimethylpropylsulfonylmethyl, ethanesulfonylmethyl, methanesulfonylmethyl, propane-1-
 sulfonylmethyl, 1*H*-indol-2-ylmethanesulfonylmethyl, 2-(1*H*-indol-3-
 yl)ethanesulfonylmethyl, 2,2,2-trifluoroethanesulfonylmethyl, benzisoxazol-3-
 15 ylmethanesulfonylmethyl, 2-*tert*-butyl-[1.3.4]thiadiazol-5-ylmethanesulfonylmethyl, 2,4,6-
 trifluorophenylmethanesulfonylmethyl, 2-pyridin-2-ylethanesulfonylmethyl, 1-ethyl-2,5-
 dioxopyrrolidin-3-ylmethanesulfonylmethyl or benzisoxazol-3-ylmethanesulfonylmethyl;
 R⁴ is hydrogen;
 R^{4'} is difluoromethyl, trifluoromethyl, or 1,1,2,2,2-pentafluoroethyl, more
 20 preferably trifluoromethyl.

[0079] (F) Yet another preferred group of compounds is that wherein R³ is -alkylene-
 SO₂-haloalkylene-heteroaryl, more preferably -alkylene-SO₂-CF₂-heteroaryl.

[0080] Within this preferred group a more preferred group is that wherein R¹ and R² are
 cyclopropylene.

25 [0081] (G) Yet another preferred group of compounds is that wherein:

R³ is 3,5-dimethylisoxazol-4-ylmethanesulfonylmethyl; 2-
 CF₃methylphenylmethane-sulfonylmethyl, 3-CF₃pyridin-2-ylmethanesulfonylmethyl, 2-F-
 furan-5-ylmethanesulfonyl-methyl, 2-methylthiazol-4-ylmethanesulfonylmethyl,
 tetrahydropyran-4-ylmethane-sulfonylmethyl, 1,1-dioxo-1λ⁶-hexahydrothiopyran-4-
 30 ylmethanesulfonylmethyl, 1-ethylpiperidin-4-ylmethanesulfonylmethyl, 2-oxo-
 tetrahydropyrimidin-4-ylmethane-sulfonylmethyl, 1-ethyl-2-oxopiperidin-4-
 ylmethanesulfonylmethyl, 1-acetylpiperidin-4-ylmethanesulfonylmethyl, 1-

- ethoxycarbonylpiperidin-4-ylmethanesulfonylmethyl, 1-methylsulfonylpiperidin-4-ylmethanesulfonylmethyl, 1-cyclopropylpiperidin-4-ylmethanesulfonylmethyl, 1-acetylazetidin-3-ylmethanesulfonylmethyl, 1-ethoxycarbonylazetidin-3-ylmethanesulfonylmethyl, 1-methylsulfonylazetidin-3-ylmethanesulfonylmethyl, 1-ethylazetidin-3-ylmethanesulfonylmethyl, 1-cyclopropylazetidin-3-ylmethanesulfonylmethyl, furan-2-ylmethanesulfonylmethyl, difluoro-(4-fluorophenyl)methanesulfonylmethyl, difluoro-(pyrazin-2-yl)methanesulfonylmethyl, difluoro-(2-difluoromethoxyphenyl)-methanesulfonylmethyl, 1-acetylpiperidin-4-ylsulfonylmethyl, 1-ethoxycarbonylpiperidin-4-ylsulfonylmethyl, 1-cyclopropylpiperidin-4-ylsulfonylmethyl, 2-(pyridin-2-yl)ethanesulfonylmethyl, 2-(pyridin-3-yl)ethanesulfonylmethyl, 2-(pyridin-4-yl)ethanesulfonylmethyl, 3-(pyridin-2-yl)propanesulfonylmethyl, 2,6-difluorophenylmethanesulfonyl, [1.3.5]triazin-2-ylmethanesulfonylmethyl, [1.3.4]thiadiazol-2-ylmethanesulfonylmethyl, oxazol-5-ylmethanesulfonylmethyl, thiazol-5-ylmethanesulfonylmethyl, 4-fluorophenylmethanesulfonylmethyl, 4-aminocarbonylphenylmethanesulfonylmethyl, 4-piperazin-4-ylphenylmethanesulfonylmethyl, 5-fluoroindol-3-ylmethanesulfonylmethyl, 4,6-difluoroindol-3-ylmethanesulfonylmethyl, 1-methylindol-3-ylmethanesulfonylmethyl, 4-fluoroindol-3-ylmethanesulfonylmethyl, 2-(5-fluoroindol-3-yl)ethanesulfonylmethyl, 2-(4,6-difluoroindol-3-yl)ethanesulfonylmethyl, 2-(1-methylindol-3-yl)ethanesulfonylmethyl, 2-(4-fluoroindol-3-yl)ethanesulfonylmethyl, 2-quinolin-3-ylethanesulfonylmethyl, 2-quinolin-2-ylethanesulfonylmethyl, isoquinolin-3-ylmethanesulfonylmethyl, 2-(isoquinolin-3-yl)ethanesulfonylmethyl, 2,4-difluoropyridin-3-ylmethanesulfonylmethyl, 3,4-difluoropyridin-4-ylmethanesulfonylmethyl, 2-(2,4-difluoropyridin-3-yl)ethanesulfonylmethyl, 2-(3,4-difluoropyridin-4-yl)ethanesulfonylmethyl, fluoro-(2,4-difluoropyridin-3-yl)methanesulfonylmethyl, fluoro-(3,4-difluoropyridin-4-yl)methanesulfonylmethyl, 2,4-diCF₃pyridin-3-ylmethanesulfonylmethyl, 3,4-diCF₃pyridin-4-ylmethanesulfonylmethyl, 2-(2,4-diCF₃pyridin-3-yl)ethanesulfonylmethyl, 2-(3,4-diCF₃pyridin-4-yl)ethanesulfonylmethyl, fluoro-(2,4-diCF₃pyridin-3-yl)methanesulfonylmethyl, fluoro-(3,4-diCF₃pyridin-4-yl)methanesulfonylmethyl, 4-F-pyridin-3-ylmethanesulfonylmethyl, 3-F-pyridin-5-ylmethanesulfonylmethyl, 2-F-pyridin-5-ylmethanesulfonylmethyl, 2-F-pyridin-3-ylmethanesulfonylmethyl, 5-F-pyridin-2-ylmethanesulfonylmethyl, 4-F-pyridin-2-ylmethanesulfonylmethyl, 4-F-1-oxopyridin-3-ylmethanesulfonylmethyl, 3-F-1-oxopyridin-5-ylmethanesulfonylmethyl, 2-F-1-oxopyridin-5-ylmethanesulfonylmethyl, 2-F-1-oxopyridin-3-ylmethanesulfonylmethyl, 5-F-1-oxopyridin-2-ylmethanesulfonylmethyl, 4-F-1-oxopyridin-2-ylmethanesulfonylmethyl, 4-

CF₃-pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-pyridin-5-ylmethane-sulfonylmethyl, 3-F-pyridin-2-ylmethanesulfonylmethyl, 2-CF₃-pyridin-3-ylmethane-sulfonylmethyl, 4-CF₃-1-oxopyridin-2-ylmethanesulfonylmethyl, 3-CF₃-1-oxopyridin-5-ylmethanesulfonylmethyl, 3-F-1-oxopyridin-2-ylmethanesulfonylmethyl, 2-CF₃-1-oxopyridin-3-ylmethanesulfonylmethyl, 5 5-CF₃-1-oxopyridin-2-ylmethanesulfonylmethyl, 2-CH₃-pyridin-6-ylmethanesulfonylmethyl, 3-CH₃-pyridin-2-ylmethanesulfonylmethyl, 4-CH₃-pyridin-3-ylmethanesulfonylmethyl, 3-CH₃-pyridin-4-ylmethanesulfonylmethyl, 2-(2-CH₃-pyridin-6-yl)ethanesulfonylmethyl, 2-(3-CF₃-pyridin-2-yl)ethanesulfonylmethyl, 2-(4-CF₃-pyridin-3-yl)ethanesulfonylmethyl, 2-(3-CF₃-pyridin-4-yl)ethanesulfonylmethyl, 2-C₂H₅-pyridin-6-ylmethanesulfonylmethyl, 3-C₂H₅-pyridin-2-ylmethanesulfonylmethyl, 4-C₂H₅-pyridin-3-ylmethanesulfonylmethyl, 3-C₂H₅-pyridin-4-ylmethanesulfonylmethyl, 2-(2-C₂H₅-pyridin-6-yl)ethanesulfonylmethyl, 2-(3-C₂H₅-pyridin-2-yl)ethanesulfonylmethyl, 2-(4-C₂H₅-pyridin-3-yl)ethanesulfonylmethyl, 2-(3-C₂H₅-pyridin-4-yl)ethanesulfonylmethyl, 2-(2-CH₃-pyridin-3-yl)ethanesulfonylmethyl, 2-CF₃-pyridin-3-ylmethanesulfonylmethyl, 2-(3-CF₃-pyridin-4-yl)ethanesulfonylmethyl, 3-CF₃-pyridin-4-ylmethanesulfonylmethyl, cinnolin-3-ylmethane-sulfonylmethyl, 2-(cinnolin-3-yl)ethanesulfonylmethyl, phthalazin-1-ylmethanesulfonylmethyl, 2-(phthalazin-1-yl)ethanesulfonylmethyl, 2-(quinoxalin-2-yl)ethanesulfonylmethyl, quinazolin-2-ylmethanesulfonylmethyl, 2-(quinazolin-2-yl)ethanesulfonylmethyl, [1,8]naphthyridin-2-ylmethanesulfonylmethyl, 2-([1,8]naphthyridin-2-yl)ethanesulfonylmethyl, 20 [1,8]naphthyridin-3-ylmethanesulfonylmethyl, 2-([1,8]naphthyridin-3-yl)ethanesulfonylmethyl, 3-Cl-pyridin-2-ylmethanesulfonylmethyl, 4-Cl-pyridin-3-ylmethanesulfonylmethyl, 3-Cl-pyridin-4-ylmethane-sulfonylmethyl, 3-F-pyridin-2-ylmethanesulfonylmethyl, 4-F-pyridin-3-ylmethanesulfonyl-methyl, 3-F-pyridin-4-ylmethanesulfonylmethyl, isoquinolin-4-ylmethanesulfonylmethyl, 6-phenylpyridin-2-ylmethanesulfonylmethyl, 3-phenylpyridin-2-ylmethanesulfonylmethyl, 4-phenylpyridin-3-ylmethanesulfonylmethyl, 3-phenylpyridin-4-ylmethanesulfonylmethyl, 2-(6-phenylpyridin-2-yl)ethanesulfonylmethyl, 2-(3-phenylpyridin-2-yl)ethanesulfonylmethyl, 2-(4-phenylpyridin-3-yl)ethanesulfonylmethyl, 2-(3-phenylpyridin-4-yl)ethanesulfonylmethyl, 6-(pyridin-2-yl)pyridin-2-ylmethanesulfonylmethyl, 3-(pyridin-2-yl)pyridin-2-ylmethane-sulfonylmethyl, 4-(pyridin-2-yl)pyridin-3-ylmethanesulfonylmethyl, 3-(pyridin-2-yl)pyridin-4-ylmethanesulfonylmethyl, 2-[6-(pyridin-2-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[3-(pyridin-2-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[4-(pyridin-2-yl)pyridin-3-yl]ethanesulfonylmethyl, 2-[3-(pyridin-2-yl)pyridin-4-yl]ethanesulfonylmethyl, 6-(pyridin-3-yl)pyridin-2-ylmethane-sulfonylmethyl, 3-(pyridin-3-yl)pyridin-2-ylmethanesulfonylmethyl,

4-(pyridin-3-yl)pyridin-3-ylmethanesulfonylmethyl, 3-(pyridin-3-yl)pyridin-4-ylmethanesulfonylmethyl, 2-[6-(pyridin-3-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[3-(pyridin-3-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[4-(pyridin-3-yl)pyridin-3-yl]ethanesulfonylmethyl, 2-[3-(pyridin-3-yl)pyridin-4-yl]ethanesulfonylmethyl, 6-(pyridin-4-yl)pyridin-2-ylmethanesulfonylmethyl, 3-(pyridin-4-yl)pyridin-2-ylmethanesulfonylmethyl, 4-(pyridin-4-yl)pyridin-3-ylmethanesulfonylmethyl, 3-(pyridin-4-yl)pyridin-4-ylmethanesulfonylmethyl, 2-[6-(pyridin-4-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[3-(pyridin-4-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[4-(pyridin-4-yl)pyridin-3-yl]ethanesulfonylmethyl, 2-[3-(pyridin-4-yl)pyridin-4-yl]ethanesulfonylmethyl, 2,2-dimethylcyclopropylmethanesulfonylmethyl, biphen-2-ylmethanesulfonylmethyl, 2-thiophen-2-ylphenylmethanesulfonylmethyl, 2-thiazol-2-ylphenylmethanesulfonylmethyl, 2-thiazol-5-ylphenylmethanesulfonylmethyl, 2-[1.2.3]thiadiazol-5-ylphenylmethanesulfonylmethyl, 2-isoxazol-5-ylphenylmethanesulfonylmethyl, 2-(1-methylpyrazol-5-yl)phenylmethanesulfonylmethyl, 2-[1.2.3]triazol-5-ylphenylmethanesulfonylmethyl, 2-[1.2.3]oxadiazol-5-ylphenylmethanesulfonylmethyl, 2-[(1.2.3)triazol-5-yl]phenylmethanesulfonylmethyl, 2-[(1.2.3)triazol-1-yl]phenylmethanesulfonylmethyl, oxazolo[5,4-b]pyridin-2-ylmethanesulfonylmethyl, oxazolo[4,5-c]pyridin-2-ylmethanesulfonylmethyl, oxazolo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, benzimidazol-5-ylmethanesulfonylmethyl, benzimidazol-4-ylmethanesulfonylmethyl, 3*H*-imidazo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, 3*H*-imidazo[4,5-c]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-3*H*-imidazo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-3*H*-imidazo[4,5-c]pyridin-2-ylmethanesulfonylmethyl, 1-CF₃-1*H*-imidazo[4,5-c]pyridin-2-ylmethanesulfonylmethyl, 1-CF₃-1*H*-imidazo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, thiazolo[5,4-b]pyridin-2-ylmethanesulfonylmethyl, thiazolo[4,5-c]pyridin-2-ylmethanesulfonylmethyl, thiazolo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, 5-CF₃thiazolo[5,4-b]pyridin-2-ylmethanesulfonylmethyl, 4-CF₃thiazolo[4,5-c]pyridin-2-ylmethanesulfonylmethyl, 7-CF₃thiazolo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-1*H*-pyrrolo[2,3-b]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-1*H*-pyrrolo[3,2-c]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-1*H*-pyrrolo[3,2-b]pyridin-2-ylmethanesulfonylmethyl, imidazo[1,2-c]pyrimidin-2-ylmethanesulfonylmethyl, 8-CF₃-imidazo[1,2-c]pyrimidin-2-ylmethanesulfonylmethyl, imidazo[1,2-a]pyrimidin-2-ylmethanesulfonylmethyl, 8-CF₃-imidazo[1,2-b]pyridazin-2-ylmethanesulfonylmethyl, imidazo[1,2-a]pyrazin-2-ylmethanesulfonylmethyl, 8-CF₃-imidazo[1,2-a]pyrazin-2-ylmethanesulfonylmethyl, pyrazolo[1,5-c]pyrimidin-2-ylmethanesulfonylmethyl, 3-CF₃-pyrazolo[1,5-c]pyrimidin-2-

- ylmethanesulfonylmethyl, 4-CF₃-pyrazolo[1,5-c]pyrimidin-2-ylmethanesulfonylmethyl, imidazo[1,2-d][1,2,4]triazin-2-methanesulfonylmethyl, 3-CF₃-imidazo[1,2-d][1,2,4]triazin-2-methanesulfonylmethyl, [1,3]benzoxazol-2-ylmethanesulfonylmethyl, 5-F-[1,3]benzoxazol-2-ylmethanesulfonylmethyl [1,3]benzoxazol-4-ylmethanesulfonylmethyl, 2-CF₃-
- 5 [1,3]benzoxazol-4-ylmethanesulfonyl-methyl, [1,3]benzoxazol-7-ylmethanesulfonylmethyl, 2-CF₃-[1,3]benzoxazol-7-ylmethane-sulfonylmethyl, [1,2]benzoxazol-3-ylmethanesulfonylmethyl, [1,2]benzoxazol-4-ylmethanesulfonylmethyl, 5-CF₃-[1,2]benzoxazol-4-ylmethanesulfonylmethyl, 3-CF₃-[1,2]benzoxazol-4-ylmethanesulfonylmethyl, 6-CF₃-[1,2]benzoxazol-7-ylmethane-sulfonylmethyl, 6-CN-
- 10 [1,2]benzoxazol-7-ylmethanesulfonylmethyl, 3-CF₃-[1,2]benzoxazol-7-ylmethanesulfonylmethyl, 5-F-[1,2]benzoxazol-3-ylmethanesulfonylmethyl, [2,3]benzoxazol-7-ylmethanesulfonylmethyl, 6-CF₃-[2,3]benzoxazol-7-ylmethanesulfonylmethyl, 1-CF₃-[2,3]benzoxazol-7-ylmethanesulfonylmethyl, 5-CF₃-[2,3]benzoxazol-4-ylmethane-sulfonylmethyl, 5-CN-[2,3]benzoxazol-4-ylmethanesulfonylmethyl, 1-CF₃-[2,3]benzoxazol-
- 15 4-ylmethanesulfonylmethyl, benzothiazol-2-ylmethanesulfonylmethyl, 5-F-benzothiazol-2-ylmethanesulfonylmethyl, benzothiazol-4-ylmethanesulfonylmethyl, 2-CF₃-benzothiazol-4-ylmethanesulfonylmethyl, benzothiazol-7-ylmethanesulfonylmethyl, 2-CF₃-benzothiazol-7-ylmethanesulfonylmethyl, [1,2]benzothiazol-3-ylmethanesulfonylmethyl, [1,2]benzothiazol-4-ylmethanesulfonylmethyl, 5-CF₃-[1,2]benzothiazol-4-ylmethanesulfonylmethyl, 3-CF₃-
- 20 [1,2]benzothiazol-4-ylmethanesulfonylmethyl, 6-CF₃-[1,2]benzothiazol-7-ylmethane-sulfonylmethyl, 6-CN-[1,2]benzothiazol-7-ylmethanesulfonylmethyl, 3-CF₃-[1,2]benzothiazol-7-ylmethanesulfonylmethyl, 5-F-[1,2]benzothiazol-3-ylmethanesulfonylmethyl, [2,3]benzothiazol-7-ylmethanesulfonylmethyl, 6-CF₃-[2,3]benzothiazol-7-ylmethane-sulfonylmethyl, 1-CF₃-[2,3]benzothiazol-7-
- 25 ylmethanesulfonylmethyl, 5-CF₃-[2,3]benzothiazol-4-ylmethanesulfonylmethyl, 5-CN-[2,3]benzothiazol-4-ylmethanesulfonylmethyl, 1-CF₃-[2,3]benzothiazol-4-ylmethanesulfonylmethyl, 4-CF₃-2-CH₃-thiazol-5-ylmethanesulfonylmethyl, 4-CF₃-thiazol-5-ylmethanesulfonylmethyl, 4-CF₃-2-phenyl-thiazol-5-ylmethanesulfonylmethyl, 5-CF₃-2-CH₃-thiazol-4-ylmethanesulfonylmethyl, 5-CF₃-thiazol-4-ylmethanesulfonylmethyl, 5-CF₃-2-
- 30 phenyl-thiazol-4-ylmethanesulfonylmethyl, 5-CH₃-thiazol-2-ylmethanesulfonylmethyl, 5-CF₃-thiazol-2-ylmethanesulfonylmethyl, 5-phenyl-thiazol-2-ylmethanesulfonylmethyl, 4-CH₃-thiazol-2-ylmethanesulfonylmethyl, 4-CF₃-thiazol-2-ylmethanesulfonylmethyl, 4-phenyl-thiazol-2-ylmethanesulfonylmethyl, 5-CH₃-2-(pyridin-2-yl)-[1,2,3]triazol-4-ylmethanesulfonylmethyl, 5-CF₃-2-(pyridin-2-yl)-[1,2,3]triazol-4-ylmethanesulfonylmethyl,

- 5-CF₃-2-(4-methylsulfonylphenyl)-[1,2,3]triazol-4-ylmethane-sulfonylmethyl, 4,5-dimethyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 5-CF₃-4-CH₃-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 4-CH₃-5-phenyl-[1,2,4]triazol-3-ylmethane-sulfonylmethyl, 5-CF₃-4-cyclopropyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 2,5-dimethyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 5-CF₃-2-CH₃-[1,2,4]triazol-3-ylmethane-sulfonylmethyl, 2-CH₃-5-phenyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 2-cyclopropyl-5-phenyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 5-CF₃-1-CH₃-[1,2,4]triazol-3-ylmethane-sulfonylmethyl, 1-CH₃-5-phenyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 5-CH₃-1-phenyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 3-CH₃-[1,2,4]oxadiazol-5-ylmethanesulfonylmethyl 3-CF₃-[1,2,4]oxadiazol-5-ylmethanesulfonylmethyl, 3-phenyl-[1,2,4]oxadiazol-5-ylmethane-sulfonylmethyl, 5-CH₃-[1,2,4]oxadiazol-3-ylmethanesulfonylmethyl, 5-CF₃-[1,2,4]oxadiazol-3-ylmethanesulfonylmethyl, 5-phenyl-[1,2,4]oxadiazol-3-ylmethanesulfonylmethyl, 2-CH₃-[1,3,4]oxadiazol-5-ylmethanesulfonylmethyl, 2-CF₃-[1,3,4]oxadiazol-5-ylmethane-sulfonylmethyl, 2-phenyl-[1,3,4]oxadiazol-5-ylmethanesulfonylmethyl, 3-CH₃-[1,2,4]thiadiazol-5-ylmethanesulfonylmethyl, 3-CF₃-[1,2,4]thiadiazol-5-ylmethanesulfonylmethyl, 3-phenyl-[1,2,4]thiadiazol-5-ylmethanesulfonylmethyl, 5-CH₃-[1,2,4]thiadiazol-3-ylmethane-sulfonylmethyl, 5-CF₃-[1,2,4]thiadiazol-3-ylmethanesulfonylmethyl, 5-phenyl-[1,2,4]thiadiazol-3-ylmethanesulfonylmethyl, 2-CH₃-[1,3,4]thiadiazol-5-ylmethanesulfonylmethyl, 2-CF₃-[1,3,4]thiadiazol-5-ylmethanesulfonylmethyl, 2-phenyl-[1,3,4]thiadiazol-5-ylmethane-sulfonylmethyl, 2,2-difluoropyrrolidinylmethanesulfonylmethyl, 3,3-difluoropyrrolidinyl-methanesulfonylmethyl, 3-CF₃-*N*-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 3-CN-*N*-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 4-CF₃-*N*-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 4-(1-CH₃-1-hydroxyethyl)-*N*-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 1,3-dimethylpyrrol-2-ylmethane-sulfonylmethyl, 4-CF₃-*N*-CH₃-pyrrol-3-ylmethanesulfonylmethyl, 4-CN-*N*-CH₃-pyrrol-3-ylmethanesulfonylmethyl, 4-CN-*N*-(3,3,3-trifluoropropyl)-pyrrol-3-ylmethanesulfonylmethyl, 2-CF₃-*N*-CH₃-pyrrol-3-ylmethanesulfonylmethyl, 2-CF₃-*N*-phenyl-pyrrol-3-ylmethane-sulfonylmethyl, 4-CF₃-pyrrol-2-ylmethanesulfonylmethyl, 4-(1-CH₃-1-hydroxyethyl)-pyrrol-2-ylmethanesulfonylmethyl, 3-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 4-CF₃-pyrrol-3-ylmethane-sulfonylmethyl, 2-CF₃-pyrrol-3-ylmethanesulfonylmethyl, 2-CF₃-*N*-CH₃-pyrrol-4-ylmethane-sulfonylmethyl, 3-CF₃-fur-2-ylmethanesulfonylmethyl, 3-CN-fur-2-ylmethanesulfonylmethyl, 3-CF₃-fur-4-ylmethanesulfonylmethyl, 3-CN-fur-4-ylmethanesulfonylmethyl, 2-CF₃-fur-3-ylmethanesulfonylmethyl, 3-CF₃-thiazol-2-

ylmethanesulfonylmethyl, 3-CN-thiazol-2-ylmethanesulfonylmethyl, 3-CF₃-thiazol-4-
 ylmethanesulfonylmethyl, 3-CN-thiazol-4-ylmethanesulfonylmethyl, 2-CF₃-thiazol-3-
 ylmethanesulfonylmethyl, *N*-CH₃-3-CF₃-1*H*-pyrazol-5-ylmethanesulfonylmethyl, *N*-CH₃-3-
 (1-CH₃-1-hydroxyethyl)-1*H*-pyrazol-5-ylmethane-sulfonylmethyl, *N*-CH₃-3-phenyl-1*H*-
 5 pyrazol-5-ylmethanesulfonylmethyl, *N*-CH₃-3-CF₃-1*H*-pyrazol-4-ylmethanesulfonylmethyl,
N-CH₃-4-CN-1*H*-pyrazol-3-ylmethanesulfonylmethyl, *N*-phenyl-4-CN-1*H*-pyrazol-3-
 ylmethanesulfonylmethyl, *N*-phenyl-3-CF₃-1*H*-pyrazol-4-ylmethanesulfonylmethyl, *N*-
 phenyl-5-CF₃-1*H*-pyrazol-4-ylmethanesulfonylmethyl, (*N*-CH₃-4-CF₃-1*H*-imidazol-2-
 ylmethane)-sulfonylmethyl, [*N*-CH₃-4-(1-CH₃-1-hydroxyethyl)-1*H*-imidazol-2-ylmethane]-
 10 sulfonylmethyl, (*N*-CH₃-4-phenyl-1*H*-imidazol-2-ylmethane)-sulfonylmethyl, *N*-CH₃-3-CF₃-
 1*H*-pyrazol-4-ylmethanesulfonylmethyl, (*N*-CH₃-2-CF₃-1*H*-imidazol-5-ylmethane)-
 sulfonylmethyl, (*N*-CH₃-2-phenyl-1*H*-imidazol-5-ylmethane)-sulfonylmethyl, (*N*-CH₃-5-CF₃-
 1*H*-imidazol-4-ylmethane)-sulfonylmethyl, (*N*-phenyl-5-CF₃-1*H*-imidazol-4-ylmethane)-
 sulfonylmethyl, 4-CN-[1,2]oxazol-5-ylmethanesulfonylmethyl 4-CN-3-phenyl-[1,2]oxazol-5-
 15 ylmethanesulfonylmethyl, 4-CN-[1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CN-5-phenyl-
 [1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CN-isothiazol-5-ylmethanesulfonylmethyl, 4-CN-
 3-phenyl-isothiazol-5-ylmethanesulfonylmethyl, 4-CN-isothiazol-3-
 ylmethanesulfonylmethyl, 4-CN-5-phenyl-isothiazol-3-ylmethane-sulfonylmethyl, 4-CF₃-
 [1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-3-CH₃-[1,2]oxazol-5-
 20 ylmethanesulfonylmethyl, 4-CF₃-3-phenyl-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-
 [1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CF₃-5-CH₃-[1,2]oxazol-3-
 ylmethanesulfonylmethyl 4-CF₃-5-phenyl-[1,2]oxazol-3-ylmethanesulfonylmethyl, 3-CF₃-
 [1,2]oxazol-4-ylmethanesulfonylmethyl, 5-CF₃-[1,2]oxazol-4-ylmethanesulfonylmethyl, 4-
 CF₃-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-3-CH₃-[1,2]oxazol-5-
 25 ylmethanesulfonylmethyl, 4-CF₃-3-phenyl-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-
 [1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CF₃-5-CH₃-[1,2]oxazol-3-
 ylmethanesulfonylmethyl, 4-CF₃-5-phenyl-[1,2]oxazol-3-ylmethanesulfonylmethyl, 3-CF₃-
 [1,2]oxazol-4-ylmethanesulfonylmethyl, 5-CF₃-[1,2]oxazol-4-ylmethanesulfonylmethyl, 4-
 CH₃-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CH₃-3-phenyl-[1,2]oxazol-5-
 30 ylmethanesulfonylmethyl, 4-CH₃-[1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CH₃-5-phenyl-
 [1,2]oxazol-3-ylmethanesulfonylmethyl, 3-CH₃-[1,2]oxazol-4-ylmethane-sulfonylmethyl, 5-
 CH₃-[1,2]oxazol-4-ylmethanesulfonylmethyl, 4-CH₃-isothiazol-5-ylmethane-sulfonylmethyl,
 4-CH₃-3-phenyl-isothiazol-5-ylmethanesulfonylmethyl, 4-CH₃-isothiazol-3-
 ylmethanesulfonylmethyl, 4-CH₃-5-phenyl-isothiazol-3-ylmethanesulfonylmethyl, 3-CH₃-

- isothiazol-4-ylmethanesulfonylmethyl, 5-CH₃-isothiazol-4-ylmethanesulfonylmethyl, 4-CF₃-2-CH₃-[1,3]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-[1,3]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-2-phenyl-[1,3]oxazol-5-ylmethanesulfonylmethyl, 5-CF₃-2-CH₃-[1,3]oxazol-4-yl-methanesulfonylmethyl, 5-CF₃-[1,3]oxazol-4-ylmethanesulfonylmethyl, 5-CF₃-2-phenyl-[1,3]oxazol-4-ylmethanesulfonylmethyl, 5-CH₃-[1,3]oxazol-2-ylmethanesulfonylmethyl, 5-CF₃-[1,3]oxazol-2-ylmethanesulfonylmethyl, 5-phenyl-[1,3]oxazol-2-ylmethane-sulfonylmethyl, 4-CH₃-[1,3]oxazol-2-ylmethanesulfonylmethyl, 4-CF₃-[1,3]oxazol-2-ylmethanesulfonylmethyl, 4-phenyl-[1,3]oxazol-2-ylmethanesulfonylmethyl, *N*-methyl-indol-2-ylmethanesulfonylmethyl, 3-CF₃-indol-2-ylmethanesulfonylmethyl, 3-CF₃-*N*-methyl-indol-2-ylmethanesulfonylmethyl, 5-fluoro-*N*-methyl-indol-2-ylmethanesulfonylmethyl, *N*-methyl-indol-3-ylmethanesulfonylmethyl, 2-CF₃-indol-3-ylmethanesulfonylmethyl, 2-CF₃-*N*-methyl-indol-3-ylmethanesulfonylmethyl, 5-fluoro-*N*-methyl-indol-3-ylmethanesulfonylmethyl, 5-CF₃-*N*-methyl-indol-4-ylmethanesulfonylmethyl, 5-CN-*N*-methyl-indol-4-ylmethane-sulfonylmethyl, 2-CF₃-*N*-methyl-indol-4-ylmethanesulfonylmethyl, 3-CF₃-*N*-methyl-indol-4-ylmethanesulfonylmethyl, 6-CF₃-*N*-methyl-indol-7-ylmethanesulfonylmethyl, 6-CN-*N*-methyl-indol-7-ylmethanesulfonylmethyl, 2-CF₃-*N*-methyl-indol-7-ylmethanesulfonylmethyl, 3-CF₃-*N*-methyl-indol-7-ylmethanesulfonylmethyl, benzofuran-2-ylmethanesulfonylmethyl, 3-CF₃-benzofuran-2-ylmethanesulfonylmethyl, 3-CN-benzofuran-2-ylmethanesulfonylmethyl, 5-F-benzofuran-2-ylmethanesulfonylmethyl, benzofuran-3-ylmethanesulfonylmethyl, 2-CF₃-benzofuran-3-ylmethanesulfonylmethyl, 2-CH₃-benzofuran-3-ylmethanesulfonylmethyl, 5-F-benzofuran-3-ylmethanesulfonylmethyl, 5-CF₃-benzofuran-4-ylmethanesulfonylmethyl, 5-CN-benzofuran-4-ylmethanesulfonylmethyl, 2-CF₃-benzofuran-4-ylmethanesulfonylmethyl, 3-CF₃-benzofuran-4-ylmethanesulfonylmethyl, 6-CF₃-benzofuran-7-ylmethanesulfonylmethyl, 6-CN-benzofuran-7-ylmethanesulfonylmethyl, 2-CF₃-benzofuran-7-ylmethanesulfonylmethyl, 3-CF₃-benzofuran-7-ylmethanesulfonylmethyl, benzothien-2-ylmethanesulfonylmethyl, (3-CF₃-benzothien-2-ylmethane)-sulfonylmethyl, (3-CN-benzothien-2-ylmethane)-sulfonylmethyl, (5-F-benzothien-2-ylmethane)-sulfonylmethyl, benzothien-3-ylmethanesulfonylmethyl, (2-CF₃-benzothien-3-ylmethane)-sulfonylmethyl, (2-CH₃-benzothien-3-ylmethane)-sulfonylmethyl, (5-fluoro-benzothien-3-ylmethane)-sulfonylmethyl, (5-CF₃-benzothien-4-ylmethane)-sulfonylmethyl, (5-CN-benzothien-4-ylmethane)-sulfonylmethyl, (2-CF₃-benzothien-4-ylmethane)-sulfonylmethyl, (3-CF₃-benzothien-4-ylmethane)-sulfonylmethyl, (6-CF₃-benzothien-7-ylmethane)-sulfonylmethyl, (6-CN-benzothien-7-ylmethane)-sulfonylmethyl,

(2-CF₃-benzothien-7-ylmethane)-sulfonylmethyl, (3-CF₃-benzothien-7-ylmethane)-sulfonylmethyl, *N*-methyl-benzimidazol-2-ylmethanesulfonylmethyl, (5-fluoro-*N*-methyl-benzimidazol-2-ylmethane)-sulfonylmethyl, (*N*-methyl-indazol-3-ylmethane)-sulfonylmethyl, (5-fluoro-*N*-methyl-indazol-3-ylmethane)-sulfonylmethyl, (2-CF₃-*N*-methyl-benzimidazol-4-ylmethane)-sulfonylmethyl, (2-CF₃-*N*-methyl-benzimidazol-7-ylmethane)-sulfonylmethyl, (*N*-methyl-indazol-4-ylmethane)-sulfonylmethyl, (5-CF₃-*N*-methyl-indazol-4-ylmethane)-sulfonylmethyl, (3-CF₃-*N*-methyl-indazol-4-ylmethane)-sulfonylmethyl, (6-CF₃-*N*-methyl-indazol-7-ylmethane)-sulfonylmethyl, (6-CN-*N*-methyl-indazol-7-ylmethane)-sulfonylmethyl, or (3-CF₃-*N*-methyl-indazol-7-ylmethane)-sulfonylmethyl.

10 [0082] (i) Within this group (G), a preferred group of compounds is that wherein:

R⁴ is hydrogen; and

R^{4'} is 1,1,2,2-tetrafluoroethyl or 1,1,2,2,2-pentafluoroethyl.

[0083] (ii) Within this group (G), another preferred group of compounds is that wherein:

R^{4'} is difluoromethyl or trifluoromethyl; and

15 R⁴ is phenyl, 2-fluorophenyl, or 2,4-difluorophenyl.

[0084] (iii) Within this group (G), yet another preferred group of compounds is that wherein:

R⁴ is difluoromethyl or trifluoromethyl; and

R^{4'} is 1,1,2,2-tetrafluoroethyl or 1,1,2,2,2-pentafluoroethyl.

20 [0085] (iv) Within this group (G), yet another preferred group of compounds is that wherein:

R⁴ is methyl or ethyl; and

R^{4'} is 1,1,2,2-tetrafluoroethyl or 1,1,2,2,2-pentafluoroethyl.

25 [0086] Within the above preferred group (G), G(i), G(ii), G(iii) and G(iv), a particularly preferred group of compounds is that wherein R¹ and R² together with the carbon atom to which they are attached form cycloalkylene, preferably R¹ and R² together with the carbon atom to which they are attached form cyclopropylene.

[0087] Within the above preferred group (G), G(i), G(ii), G(iii) and G(iv), another particularly preferred group of compounds is that wherein R¹ and R² together with the carbon atom to which they are attached form piperidin-4-yl substituted at the nitrogen with ethyl, trifluoroethyl or cyclopropyl.

30

[0088] Within the above preferred group (G), G(i), G(ii), G(iii) and G(iv), yet another particularly preferred group of compounds is that wherein R¹ and R² together with the carbon atom to which they are attached form tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-dioxohexahydrothiopyran-4-yl.

- 5 [0089] Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise.

[0090] Compounds of Formula (I) where R¹ and R² together form cyclopropylene and R³, R⁴, and R^{4'} are as defined in Table I below are:

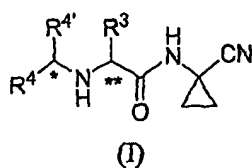


Table I

Cpd #	Stereochem at (*C,**C)	R ^{4'}	R ³	R ⁴
1	(S,R)	CF ₃	4-CF ₃ -pyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
2	(S,R)	CF ₃	pyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
3	(S,R)	CF ₃	pyridazin-3-ylmethanesulfonylmethyl	4-F-phenyl
4	(S,R)	CF ₃	2-CF ₃ -furan-5-ylmethanesulfonylmethyl	4-F-phenyl
5	(S,R)	CF ₃	pyrimidin-5-ylmethanesulfonylmethyl	4-F-phenyl
6	(S,R)	CF ₃	2-CH ₃ -thiazol-4-ylmethanesulfonylmethyl	4-F-phenyl
7	(S,R)	CF ₃	pyridin-4-ylmethanesulfonylmethyl	4-F-phenyl
8	(S,R)	CF ₃	pyrimidin-4-ylmethanesulfonylmethyl	4-F-phenyl
9	(S,R)	CF ₃	2-(1-oxopyrrol-1-yl)ethanesulfonylmethyl	4-F-phenyl
10	(R,R)	CF ₃	pyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
11	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	3-F-phenyl
12	(S,R)	CF ₃	3,3,3-trifluoropropane-1-sulfonylmethyl	4-F-phenyl
13	(S,R)	CF ₃	2-CF ₃ -pyridin-5-ylmethanesulfonylmethyl	4-F-phenyl
14	(S,R)	CF ₃	4-[1.2.4]-triazol-1-ylphenylmethane-sulfonylmethyl	4-F-phenyl

Cpd #	Stereochem at (*C,**C)	R ⁴	R ³	R ⁴
15	(S,R)	CF ₃	2-(2-oxo-2,3-dihydrobenzimidazol-1-yl)-ethanesulfonylmethyl	4-F-phenyl
16	(S,R)	CF ₃	5-oxopyrrolidin-2-ylmethanesulfonylmethyl	4-F-phenyl
17	(S,R)	CF ₃	2-F-pyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
18	(S,R)	CF ₃	3-CH ₃ -oxetan-3-ylmethanesulfonylmethyl	4-F-phenyl
19	(S,R)	CF ₃	2-phenylethanesulfonylmethyl	4-F-phenyl
20	(R,R)	CF ₃	3,3,3-trifluoropropane-1-sulfonylmethyl	4-F-phenyl
21	(S,R)	CF ₃	fluoro-pyridin-2-ylmethanesulfonylmethyl	4-F-phenyl
22	(S,R)	CF ₃	fluoro-pyrazin-2-ylmethanesulfonylmethyl	4-F-phenyl
23	(S,R)	CF ₃	difluoro-pyridin-2-ylmethanesulfonylmethyl	4-F-phenyl
24	(S,R)	CF ₃	difluoro-pyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
25	(S,R)	CF ₃	quinolin-2-ylmethanesulfonylmethyl	4-F-phenyl
26	(S,R)	CF ₃	benzo[1.2.5]thiadiazol-4-yl-methanesulfonylmethyl	4-F-phenyl
27	(S,R)	CF ₃	benzothiazol-2-ylmethanesulfonylmethyl	4-F-phenyl
28	(S,R)	CF ₃	5-methylisoxazol-3-ylmethanesulfonylmethyl	4-F-phenyl
29	(S,R)	CF ₃	2-methylpropylsulfonylmethyl	4-F-phenyl
30	(S,R)	CF ₃	cyclobutylmethanesulfonylmethyl	4-F-phenyl
31	(S,R)	CF ₃	2,6-difluorophenylmethanesulfonylmethyl	4-F-phenyl
32	(S,R)	CF ₃	2,4-difluorophenylmethanesulfonylmethyl	4-F-phenyl
33	(S,R)	CF ₃	quinolin-3-ylmethanesulfonylmethyl	4-F-phenyl
34	(S,R)	CF ₃	4,4,4-trifluorobutyl-1-sulfonylmethyl	4-F-phenyl
35	(S,R)	CF ₃	2-CF ₃ -phenylmethanesulfonylmethyl	4-F-phenyl
36	(S,R)	CF ₃	2-CF ₃ O-phenylmethanesulfonylmethyl	4-F-phenyl
37	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	3,5-diF-phenyl
38	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,5-diF-phenyl

Cpd #	Stereochem at (*C,**C)	R ^{4'}	R ³	R ⁴
39	(S,R)	CF ₃	2-pyridin-2-ylethanesulfonylmethyl	4-F-phenyl
40	(S,R)	CF ₃	2-pyridin-3-ylethanesulfonylmethyl	4-F-phenyl
41	(S,R)	CF ₃	quinolin-8-ylmethanesulfonylmethyl	4-F-phenyl
42	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,3-diF-phenyl
43	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,4-diF-phenyl
44	(S,R)	CF ₃	5-methyl-3-phenylisoxazol-4-yl-methanesulfonylmethyl	4-F-phenyl
45	(S,R)	CF ₃	4-methyl-2-phenyl-[1.2.3]triazol-5-ylmethanesulfonylmethyl	4-F-phenyl
46	(S,R)	CF ₃	2-cyanophenylmethanesulfonylmethyl	4-F-phenyl
47	(S,R)	CF ₃	3-methoxycarbonylphenylmethanesulfonylmethyl	4-F-phenyl
48	(S,R)	CHF ₂	cyclopropylmethanesulfonylmethyl	4-F-phenyl
49	(RS,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2-Cl-pyridin-5-yl
50	(S,R)	CF ₂ C F ₃	pyridin-2-ylmethanesulfonylmethyl	4-F-phenyl
51	(S,R)	CF ₂ C F ₃	1-oxopyridin-2-ylmethanesulfonylmethyl	4-F-phenyl
52	(S,R)	CF ₂ C F ₃	pyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
53	(S,R)	CF ₂ C F ₃	1-oxopyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
54	(S,R)	CF ₂ C F ₃	cyclopropylmethanesulfonylmethyl	4-F-phenyl
55	(S,R)	CF ₃	quinoxalin-2-ylmethanesulfonylmethyl	4-F-phenyl
56	(S,R)	CF ₃	tetrahydropyran-2(RS)-ylmethanesulfonylmethyl	4-F-phenyl
57	(S,R)	CF ₃	2,6-dichlorophenylmethanesulfonylmethyl	4-F-phenyl
58	(S,R)	CF ₃	3-methoxycarbonylfuran-2-yl-methanesulfonylmethyl	4-F-phenyl

Cpd #	Stereochem at (*C,**C)	R ^{4'}	R ³	R ⁴
59	(S,R)	CF ₂ C F ₃	5-methylisoxazol-3-ylmethanesulfonylmethyl	4-F-phenyl
60	(S,R)	CF ₃	2,2-dimethylpropylsulfonylmethyl	4-F-phenyl
61	(R,R)	CF ₂ C F ₃	pyridin-3-ylmethanesulfonylmethyl	4-F-phenyl
62	(S,R)	CF ₃	ethanesulfonylmethyl	4-F-phenyl
63	(R,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,5-diF-phenyl
64	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,6-diF-phenyl
65	(R,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,6-diF-phenyl
66	(R,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,3-diF-phenyl
67	(R,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,4-diF-phenyl
68	(S,R)	CF ₃	methanesulfonylmethyl	4-F-phenyl
69	(S,R)	CF ₃	propane-1-sulfonylmethyl	4-F-phenyl
70	(S,R)	CF ₃	1 <i>H</i> -indol-2-ylmethanesulfonylmethyl	4-F-phenyl
71	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2-F-phenyl
72	(R,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2-F-phenyl
73	(S,R)	CF ₃	pyridin-2-ylmethanesulfonylmethyl	3,4-diF-phenyl
74	(S,R)	CF ₃	pyridin-3-ylmethanesulfonylmethyl	3,4-diF-phenyl
75	(S,R)	CF ₃	2-(1 <i>H</i> -indol-3-yl)ethanesulfonylmethyl	4-F-phenyl
76	(S,R)	CF ₃	tetrahydropyran-4-ylmethanesulfonylmethyl	4-F-phenyl
77	(S,R)	CF ₃	1-oxopyridin-2-ylmethanesulfonylmethyl	2-F-phenyl
78	(R,R)	CF ₃	1-oxopyridin-2-ylmethanesulfonylmethyl	2-F-phenyl
79	(S,R)	CF ₃	pyridin-2-ylmethanesulfonylmethyl	2-F-phenyl

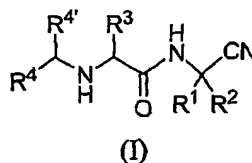
Cpd #	Stereochem at (*C,**C)	R ⁴	R ³	R ⁴
80	(R,R)	CF ₃	pyridin-2-ylmethanesulfonylmethyl	2-F-phenyl
81	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,3,4-triF-phenyl
82	(R,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,3,4-triF-phenyl
83	(S,R)	CF ₃	2,2,2-trifluoroethanesulfonylmethyl	2-F-phenyl
84	(S,R)	CF ₃	benzisoxazol-3-ylmethanesulfonylmethyl	2-F-phenyl
85	(RS,R)	CF ₃	cyclopropylmethanesulfonylmethyl	3-OH-6-CH ₃ -pyridin-2-yl
86	(S,R)	CF ₃	2-tert-butyl-[1.3.4]thiadiazol-5-ylmethanesulfonylmethyl	4-F-phenyl
87	(S,R)	CF ₃	2,4,6-trifluorophenylmethanesulfonylmethyl	4-F-phenyl
88	(S,R)	CF ₂ C F ₃	2-pyridin-2-ylethanesulfonylmethyl	4-F-phenyl
89	(S,R)	CF ₃	1-ethyl-2,5-dioxopyrrolidin-3-ylmethanesulfonylmethyl	4-F-phenyl
90	(S,R)	CF ₃	benzisoxazol-3-ylmethanesulfonylmethyl	4-F-phenyl
91	(S,R)	CF ₃	cyclopropylmethanesulfonylmethyl	2,4,5-triF-phenyl
92	(S,S)	CF ₃	2-cyclopropylmethylsulfonyl ethyl	4-F-phenyl
93	(S,S)	CF ₃	2-methylsulfonyl ethyl	4-F-phenyl
94	(S,S)	CF ₃	2-phenylsulfonyl ethyl	4-F-phenyl
95	(S,S)	CF ₃	2-(4-trifluoromethylphenylsulfonyl)ethyl	4-F-phenyl
96	(S,S)	CF ₃	2-(4-methylsulfonylphenylsulfonyl)ethyl	4-F-phenyl
97	(S,R)	CF ₃	butylsulfonylmethyl	4-F-phenyl
98	(S,R)	CF ₃	pentylsulfonylmethyl	4-F-phenyl
99	(S,R)	CF ₃	hexylsulfonylmethyl	4-F-phenyl
100	(S,R)	CF ₃	heptylsulfonylmethyl	4-F-phenyl
101	(S,R)	CF ₃	3-phenylisoxazol-5-ylmethylsulfonylmethyl	4-F-phenyl

Cpd #	Stereochem at (*C,**C)	R ^{4'}	R ³	R ⁴
102	(S,R)	CF ₃	5-phenyloxazol-4-ylmethylsulfonylmethyl	4-F-phenyl
103	(S,R)	CF ₃	[1,2,4]oxadiazol-3-ylmethylsulfonylmethyl	4-F-phenyl
104	(S,R)	CF ₃	5-phenyl[1,2,4]oxadiazol-3-ylmethylsulfonylmethyl	4-F-phenyl
105	(S,R)	CF ₃	5-thiophen-2-yl[1,2,4]oxadiazol-3-ylmethylsulfonylmethyl	4-F-phenyl
106	(S,R)	CF ₃	3-thiophen-5-yl[1,2,4]oxadiazol-3-ylmethylsulfonylmethyl	4-F-phenyl
107	(S,R)	CF ₃	3,5-dimethylisooxadiazol-4-ylmethylsulfonylmethyl	4-F-phenyl
108	(S,R)	CF ₃	6-methylpyridin-2-ylmethylsulfonylmethyl	4-F-phenyl
109	(S,R)	CF ₃	3-trifluoromethyl-pyridin-4-ylmethanesulfonylmethyl	4-F-phenyl
110	(S,R)	CF ₃	cyclopropylmethylsulfonylmethyl	2,4,6-triF-phenyl
111	(R,R)	CF ₃	cyclopropylmethylsulfonylmethyl	2,4,6-triF-phenyl
112	(R)	CF ₂ C HF ₂	cyclopropylmethylsulfonylmethyl	hydrogen
113	(RS,R)	CF ₂ C HF ₂	3-trifluorobenzylsulfonylmethyl	2,4-diF-phenyl
114	(S,R)	CF ₂ C HF ₂	3-trifluorobenzylsulfonylmethyl	2,4-diF-phenyl
115	(S,R)	CF ₃	2-(2-oxoindol-1-yl)ethylsulfonylmethyl	4-F-phenyl
116	(S,R)	CF ₃	2-(2,3-dioxoindol-1-yl)ethylsulfonylmethyl	4-F-phenyl
117	(S,R)	CF ₃	4-methylsulfonylbenzylsulfonylmethyl	2,4-diF-phenyl
118	(S,R)	CF ₃	3-methylsulfonylbenzylsulfonylmethyl	2,4-diF-phenyl
119	(R,R)	CF ₃	3-methylsulfonylbenzylsulfonylmethyl	2,4-diF-phenyl
120	(R,R)	CF ₃	2-cyanobenzylsulfonylmethyl	2,4-diF-phenyl

Cpd #	Stereochem at (*C,**C)	R ¹	R ³	R ⁴
121	(S,R)	CF ₃	2-cyanobenzylsulfonylmethyl	2,4-diF-phenyl
122	(S,R)	CF ₃	2-methylsulfonylbenzylsulfonylmethyl	2,4-diF-phenyl
123	(R,R)	CF ₃	2-methylsulfonylbenzylsulfonylmethyl	2,4-diF-phenyl
124	(R,R)	CF ₃	4-methylsulfonylbenzylsulfonylmethyl	2,4-diF-phenyl
125	(S,R)	CF ₃	4-trifluoromethylpyridin-3-ylsulfonylmethyl	2,4-diF-phenyl
126	(R,R)	CF ₃	2-trifluoromethylbenzylsulfonylmethyl	2,4-diF-phenyl
127	(S,R)	CF ₃	2-trifluoromethylbenzylsulfonylmethyl	2,4-diF-phenyl
128	(S,R)	CF ₃	phenylsulfonylmethyl	4-F-phenyl
129	(S,R)	CF ₃	2-methylsulfonylbenzylsulfonylmethyl	4-F-phenyl
130	(S,R)	CF ₃	4-methylsulfonylbenzylsulfonylmethyl	4-F-phenyl
131	(S,R)	CF ₃	3-methylsulfonylbenzylsulfonylmethyl	4-F-phenyl
132	(S,R)	CF ₃	2-(2-oxo-imidazolidin-1-yl)-ethanesulfonylmethyl	4-F-phenyl
133	(S,R)	CF ₃	2-(2-oxo-imidazolidin-1-yl)-ethanesulfonylmethyl	2,4-diF-phenyl
134	(S,R)	CF ₃	2-[4-(4-fluorophenyl)-2-trifluoromethyl-imidazol-1-yl]-ethanesulfonylmethyl	2,4-diF-phenyl
135	(S,R)	CF ₃	2-[4-(4-fluorophenyl)-2-trifluoromethyl-imidazol-1-yl]-ethanesulfonylmethyl	4-F-phenyl
136	(S,R)	CF ₃	2-[5-(4-fluorophenyl)-2-trifluoromethyl-imidazol-1-yl]-ethanesulfonylmethyl	4-F-phenyl
137	(S,R)	CF ₃	2-(2-trifluoromethylimidazol-1-yl)ethanesulfonylmethyl	4-F-phenyl
138	(S,R)	CF ₃	2-(2-trifluoromethylimidazol-1-yl)ethanesulfonylmethyl	2,4-diF-phenyl
139	(S,R)	CF ₃	cyclopropylmethylsulfonylmethyl	tetrahydropyr

Cpd #	Stereochem at (*C,**C)	R ^{4'}	R ³	R ⁴
				an-4-yl
140	(S,R)	CF ₃	2-(2-oxo-pyrrolidin-1-yl)-ethanesulfonylmethyl	4-F-phenyl
141	(S,R)	CF ₃	2-(4-oxo-5-aza-benzospiro[2.4]hept-6-en-5-yl)-ethanesulfonylmethyl	4-F-phenyl
142	(S,R)	CF ₃	cyclopropylmethylsulfonylmethyl	4-Cl-phenyl

and compounds of Formula (I) R¹, R², R³, R⁴ and R^{4'} are as defined in Table II below are:



5

Table II

Cpd #	Stereochem at (*C,**C)	R ¹ and R ²	R ^{4'}	R ³	R ⁴
143	(S,R)	cyclopentylene	CF ₃	pyridine-3-ylmethanesulfonylmethyl	4-Fphenyl
144	(S,R)	cyclobutylene	CF ₃	pyridine-3-ylmethanesulfonylmethyl	4-Fphenyl
145	(S,R)	CH ₃ and CH ₃	CF ₃	pyridine-3-ylmethanesulfonylmethyl	4-Fphenyl
146	(S,R)	cyclobutylene	CF ₃	cyclopropylmethanesulfonylmethyl	4-Fphenyl
147	(S,R)	CH ₃ and CH ₃	CF ₃	4-trifluoromethylpyridin-3-ylmethanesulfonylmethyl	4-Fphenyl

and are named:

10

N-(1-cyanocyclopropyl)-3-(4-trifluoromethylpyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
N-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

- N*-(1-cyanocyclopropyl)-3-pyridan-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylfuran-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- 5 *N*-(1-cyanocyclopropyl)-3-pyrimidin-5-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(2-methylthiazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-pyridin-4-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 10 *N*-(1-cyanocyclopropyl)-3-pyrimidin-4-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-[2-(1-oxopyrrol-1-yl)ethanesulfonyl]-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 15 *N*-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*R*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-3-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(3,3,3-trifluoropropane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 20 *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylpyridin-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- N*-(1-cyanocyclopropyl)-3-(4-[1.2.4]-triazol-1-ylphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- 25 *N*-(1-cyanocyclopropyl)-3-[2-(2-oxo-2,3-dihydrobenzimidazol-1-yl)ethanesulfonyl]-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(5-oxo-pyrrolidin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylaminopropionamide;
- N*-(1-cyanocyclopropyl)-3-(2-fluoropyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylaminopropionamide;
- 30 *N*-(1-cyanocyclopropyl)-3-(3-methyloxetan-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(2-phenylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

- N*-(1-cyanocyclopropyl)-3-(3,3,3-trifluoropropane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(fluoropyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 5 *N*-(1-cyanocyclopropyl)-3-(fluoropyrazin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(difluoropyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(difluoropyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 10 *N*-(1-cyanocyclopropyl)-3-(quinolin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(benzo[1.2.5]thiadiazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 15 *N*-(1-cyanocyclopropyl)-3-(benzothiazol-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(5-methylisoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(2-methylpropylsulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 20 *N*-(1-cyanocyclopropyl)-3-(cyclobutylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(2,6-difluorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 25 *N*-(1-cyanocyclopropyl)-3-(2,4-difluorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(quinolin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(4,4,4-trifluorobutyl-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 30 *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- N*-(1-cyanocyclopropyl)-3-(2-trifluoromethoxyphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;

- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,5-difluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,5-difluorophenylethylamino)propionamide;
- 5 *N*-(1-cyanocyclopropyl)-3-(2-pyridin-2-ylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(2-pyridin-3-ylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- 10 *N*-(1-cyanocyclopropyl)-3-(quinolin-8-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,3-difluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,4-difluorophenylethylamino)propionamide;
- 15 *N*-(1-cyanocyclopropyl)-3-(5-methyl-3-phenylisoxazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- N*-(1-cyanocyclopropyl)-3-(4-methyl-2-phenyl-[1.2.3]triazol-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)-propionamide;
- N*-(1-cyanocyclopropyl)-3-(2-cyanophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- 20 *N*-(1-cyanocyclopropyl)-3-(3-methoxycarbonylphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2-difluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- 25 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*RS*)-2-chloropyridin-5-ylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylpropylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylpropylamino)-propionamide;
- 30 *N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylpropylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylpropylamino)-propionamide;

- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylpropylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(quinoxalin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 5 *N*-(1-cyanocyclopropyl)-3-(tetrahydropyran-2*RS*-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- N*-(1-cyanocyclopropyl)-3-(2,6-dichlorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(3-methoxycarbonylfuran-2*RS*-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- 10 *N*-(1-cyanocyclopropyl)-3-(5-methylisoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylpropylamino)-propionamide;
- N*-(1-cyanocyclopropyl)-3-(2,2-dimethylpropylsulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 15 *N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*R*)-4-fluorophenylpropylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(ethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,5-difluorophenylethylamino)propionamide;
- 20 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,6-difluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,6-difluorophenylethylamino)propionamide;
- 25 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,3-difluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,4-difluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(methanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- 30 *N*-(1-cyanocyclopropyl)-3-(propane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(1*H*-indol-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-fluorophenylethylamino)propionamide;
- 5 *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,4-difluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,4-difluorophenylethylamino)propionamide;
- 10 *N*-(1-cyanocyclopropyl)-3-[2-(1*H*-indol-3-yl)ethanesulfonyl]-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(tetrahydropyran-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide;
- 15 *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide;
- 20 *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,3,4-trifluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,3,4-trifluorophenylethylamino)propionamide;
- 25 *N*-(1-cyanocyclopropyl)-3-(2,2,2-trifluoroethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(benzisoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide;
- N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(3-hydroxy-6-methyl-pyridin-2-yl)-ethylamino]-propionamide;
- 30 *N*-(1-cyanocyclopropyl)-3-(2-*tert*-butyl-[1.3.4]-thiadiazol-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(2,4,6-trifluorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

- N*-(1-cyanocyclopropyl)-3-(2-pyridin-2-ylethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylpropylamino)propionamide;
- N*-(1-cyanocyclopropyl)-3-(1-ethyl-2,5-dioxopyrrolidin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- 5 *N*-(1-cyanocyclopropyl)-3-(benzoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
- N*-(1-cyano-cyclopropyl)-4-cyclopropylmethanesulfonyl-2(*S*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-butyramide;
- N*-(1-cyano-cyclopropyl)-4-methanesulfonyl-2(*S*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-butyramide;
- 10 4-benzenesulfonyl-*N*-(1-cyano-cyclopropyl)-2(*S*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-butyramide;
- N*-(1-cyano-cyclopropyl)-2(*S*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-4-(4-trifluoromethyl-benzenesulfonyl)-butyramide;
- 15 *N*-(1-cyano-cyclopropyl)-4-(4-methanesulfonyl-benzenesulfonyl)-2(*S*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-butyramide;
- 3-(butane-1-sulfonyl)-*N*-(1-cyano-cyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(pentane-1-sulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 20 *N*-(1-cyano-cyclopropyl)-3-(hexane-1-sulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(heptane-1-sulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 25 *N*-(1-cyano-cyclopropyl)-3-(3-phenyl-isoxazol-5-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(5-phenyl-oxazol-4-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-([1,2,4]oxadiazol-3-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 30 *N*-(1-cyano-cyclopropyl)-3-(5-phenyl-[1,2,4]oxadiazol-3-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(5-thiophen-2-yl-[1,2,4]oxadiazol-3-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;

- N*-(1-cyano-cyclopropyl)-3-(3-thiophen-2-yl-[1,2,4]oxadiazol-5-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(3,5-dimethyl-isoxazol-4-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 5 *N*-(1-cyano-cyclopropyl)-3-(6-methyl-pyridin-2-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(2,4,6-trifluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*R*)-(2,4,6-trifluoro-phenyl)-ethylamino]-propionamide;
- 10 *N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-(2,2,3,3-tetrafluoro-propylamino)-propionamide;
- N*-(1-cyano-cyclopropyl)-2(*R*)-[1-(2,4-difluoro-phenyl)-2,2,3,3,3-pentafluoro-propylamino]-3-(2-trifluoromethyl-phenylmethanesulfonyl)-propionamide;
- 15 *N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,3,3,3-pentafluoro-propylamino]-3-(2-trifluoromethyl-phenylmethanesulfonyl)-propionamide;
- N*-(1-cyano-cyclopropyl)-3-[2-(2-oxo-2,3-dihydro-indol-1-yl)-ethanesulfonyl]-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-[2-(2,3-dioxo-2,3-dihydro-indol-1-yl)-ethanesulfonyl]-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 20 *N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoro-ethylamino]-3-(4-methanesulfonyl-phenylmethanesulfonyl)-propionamide;
- N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoro-ethylamino]-3-(3-methanesulfonyl-phenylmethanesulfonyl)-propionamide;
- 25 *N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*R*)-(2,4-difluoro-phenyl)-2,2,2-trifluoro-ethylamino]-3-(3-methanesulfonyl-phenylmethanesulfonyl)-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(2-cyano-phenylmethanesulfonyl)-2(*R*)-[1(*R*)-(2,4-difluoro-phenyl)-2,2,2-trifluoro-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(2-cyano-phenylmethanesulfonyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoro-ethylamino]-propionamide;
- 30 *N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoro-ethylamino]-3-(2-methanesulfonyl-phenylmethanesulfonyl)-propionamide;
- N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*R*)-(2,4-difluoro-phenyl)-2,2,2-trifluoro-ethylamino]-3-(2-methanesulfonyl-phenylmethanesulfonyl)-propionamide;

- N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*R*)-(2,4-difluoro-phenyl)-2,2,2-trifluoroethylamino]-3-(4-methanesulfonyl-phenylmethanesulfonyl)-propionamide;
- N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoroethylamino]-3-(4-trifluoromethyl-pyridin-3-ylmethanesulfonyl)-propionamide;
- 5 *N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*R*)-(2,4-difluoro-phenyl)-2,2,2-trifluoroethylamino]-3-(2-trifluoromethyl-phenylmethanesulfonyl)-propionamide;
- N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoroethylamino]-3-(2-trifluoromethyl-phenylmethanesulfonyl)-propionamide;
- 10 3-benzenesulfonyl-*N*-(1-cyano-cyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(2-methanesulfonyl-phenylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-(4-methanesulfonyl-phenylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 15 *N*-(1-cyano-cyclopropyl)-3-(3-methanesulfonyl-phenylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- N*-(1-cyano-cyclopropyl)-3-[2-(2-oxo-imidazolidin-1-yl)-ethanesulfonyl]-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 20 *N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoroethylamino]-3-[2-(2-oxo-imidazolidin-1-yl)-ethanesulfonyl]-propionamide;
- N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoroethylamino]-3-{2-[4-(4-fluoro-phenyl)-2-trifluoromethyl-imidazol-1-yl]-ethanesulfonyl}-propionamide;
- N*-(1-cyano-cyclopropyl)-3-{2-[4-(4-fluoro-phenyl)-2-trifluoromethyl-imidazol-1-yl]-ethanesulfonyl}-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 25 *N*-(1-cyano-cyclopropyl)-3-{2-[5-(4-fluoro-phenyl)-2-trifluoromethyl-imidazol-1-yl]-ethanesulfonyl}-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;
- 30 *N*-(1-cyano-cyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-3-[2-(2-trifluoromethyl-benzimidazol-1-yl)-ethanesulfonyl]-propionamide;
- N*-(1-cyano-cyclopropyl)-2(*R*)-[1(*S*)-(2,4-difluoro-phenyl)-2,2,2-trifluoroethylamino]-3-[2-(2-trifluoromethyl-benzimidazol-1-yl)-ethanesulfonyl]-propionamide;

N-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1-(tetrahydro-pyran-4-yl)-ethylamino]-propionamide;

N-(1-cyano-cyclopropyl)-3-[2-(2-oxo-pyrrolidin-1-yl)-ethanesulfonyl]-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;

5 *N*-(1-cyano-cyclopropyl)-3-[2-(2-oxo-pyrrolidin-1-yl)-ethanesulfonyl]-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;

2(*R*)-[1(*S*)-(4-chloro-phenyl)-2,2,2-trifluoro-ethylamino]-*N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-propionamide;

10 *N*-(1-cyano-cyclopentyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;

N-(1-cyano-cyclobutyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;

N-(cyano-dimethyl-methyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide;

15 *N*-(1-cyano-cyclobutyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide; and

N-(cyano-dimethyl-methyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-3-(4-trifluoromethyl-pyridin-3-ylmethanesulfonyl)-propionamide.

20 GENERAL SYNTHETIC SCHEME

[0091] Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

[0092] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.),
 25 Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's
 30 Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be

synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

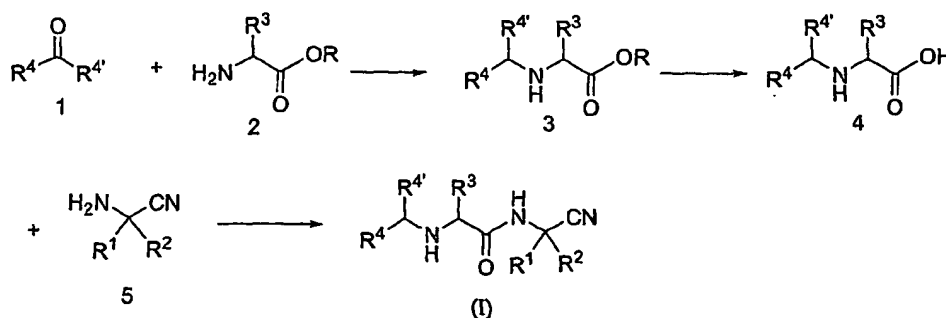
[0093] The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration,
 5 distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0094] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient)
 10 temperature, e.g., about 20 °C.

[0095] In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for
 15 examples see T.W. Greene and P. G. M. Wuts in "*Protective Groups in Organic Chemistry*" John Wiley and Sons, 1999.

[0096] Compounds of Formula (I) where R¹, R², R³, R⁴ and R^{4'} are as defined in the Summary of the Invention can be prepared by proceeding as in Reaction Scheme 1 below.

20

Scheme 1

[0097] Reaction of a ketone of formula 1 where R⁴ and R^{4'} are as defined in the Summary
 25 of the Invention with an α -amino ester of formula 2 where R is a carboxy protecting group, preferably an alkyl group, preferably methyl, and R³ is as defined in the Summary of the Invention under reductive amination reaction conditions provide a compound of formula 3.

The reaction is carried out in the presence of a suitable dehydrating agent such as TiCl_4 , and the like, in the presence of a base such as diisopropylethylamine, pyridine, and the like and in a suitable organic solvent such as methylene chloride to give an imine. The imine is reduced with a suitable reducing agent such as sodium borohydride, sodium cyanoborohydride, and the like in a suitable organic solvent such as methanol, ethanol, and the like.

[0098] Compounds of formula 1 such as 2,2,2-trifluoromethylacetophenone and 2,2,2,4'-tetrafluoroacetophenone commercially available. Others can be prepared by methods well known in the art. α -Amino esters of formula 2 can be prepared by methods well known in the art.

10 [0099] Hydrolysis of the ester group in compound 3 provides a compound of formula 4. The hydrolysis conditions depend on the nature of the protecting group. For example, when R is alkyl the hydrolysis is carried out under aqueous basic hydrolysis reaction conditions to give the corresponding acid of formula 4. The reaction is typically carried out with cesium carbonate, lithium hydroxide, and the like in an aqueous alcohol such as methanol, ethanol,
15 and the like.

[0100] Compound 4 is then reacted with an α -aminoacetonitrile of formula 5 to give a compound of Formula (I). The reaction is typically carried out in the presence of a suitable coupling agent e.g., benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), or 1,3-dicyclohexyl-carbodiimide (DCC), optionally in the presence of 1-hydroxybenzotriazole (HOBT), and a base such as *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like. The reaction is typically carried out at 20 to 30 °C, preferably at about 25 °C,
25 and requires 2 to 24 h to complete. Suitable reaction solvents are inert organic solvents such as halogenated organic solvents (e.g., methylene chloride, chloroform, and the like), acetonitrile, *N,N*-dimethylformamide, ethereal solvents such as tetrahydrofuran, dioxane, and the like.

[0101] Alternatively, the above coupling step can be carried out by first converting 4 into
30 an active acid derivative such as succinimide ester and then reacting it with an amine of formula 5. The reaction typically requires 2 to 3 h to complete. The conditions utilized in this reaction depend on the nature of the active acid derivative. For example, if it is an acid

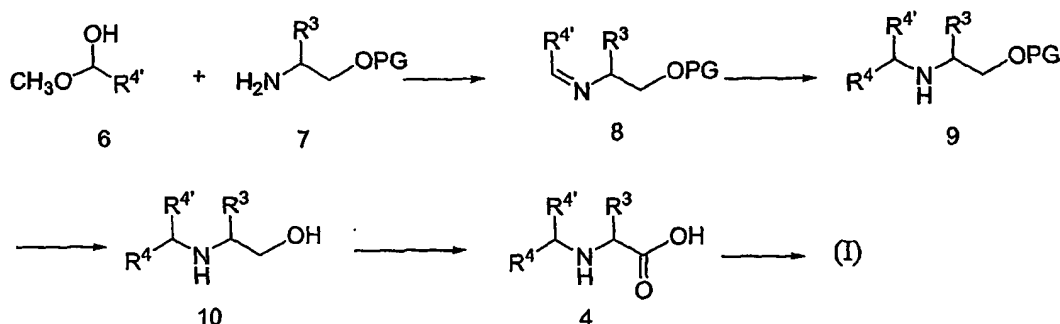
chloride derivative of 4, the reaction is carried out in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, pyridine, and the like). Suitable reaction solvents are polar organic solvents such as acetonitrile, *N,N*-dimethylformamide, dichloromethane, or any suitable mixtures thereof.

- 5 [0102] It will be apparent to a person skilled in the art, that compounds of Formula (I) can also be prepared by first condensing 5 with the *N*-protected amino acid of formula 2 where R is hydrogen followed by removal of the amino protecting group and reacting the free amino compound with a compound of formula 1 as described in Scheme 1 above. Suitable amino acid protecting groups and reaction conditions for putting them on and removing them can be found in Greene, T.W.; and Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*; John Wiley & Sons, Inc. 1999.

[0103] Alternatively, a compound of Formula (I) where R^1 , R^2 , R^3 , R^4 and $R^{4'}$ are as defined in the Summary of the Invention can be prepared as illustrated and described in Scheme 2 below.

15

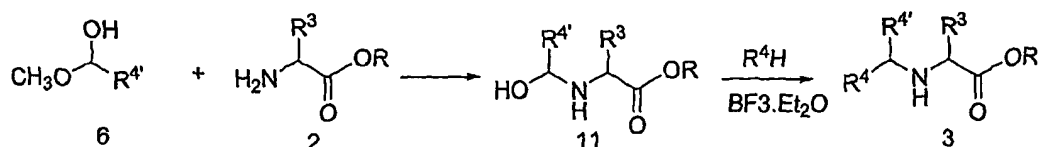
Scheme 2



- [0104] Reaction of a compound of formula 7 where R^3 is as defined in the Summary of the Invention and PG is a suitable oxygen protecting group with a hemiacetal of formula 6 provides an imine compound of formula 8. Treatment of 8 with an organolithium compound of formula R^4Li where R^4 is as defined in the Summary of the Invention provides compound 9. Removal of the oxygen protecting group, followed by oxidation of the resulting alcohol 10 provides a compound of formula 4 which is then converted to a compound of Formula (I) as described in Scheme 1 above. Suitable oxygen protecting groups and reaction conditions for putting them on and removing them can be found in Greene, T.W.; and Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*; John Wiley & Sons, Inc. 1999.

[0105] Alternatively, a compound of Formula (I) where R^1 , R^2 , R^3 , R^4 , and $R^{4'}$ are as defined in the Summary of the Invention and can be prepared as illustrated and described in Scheme 3 below.

Scheme 3



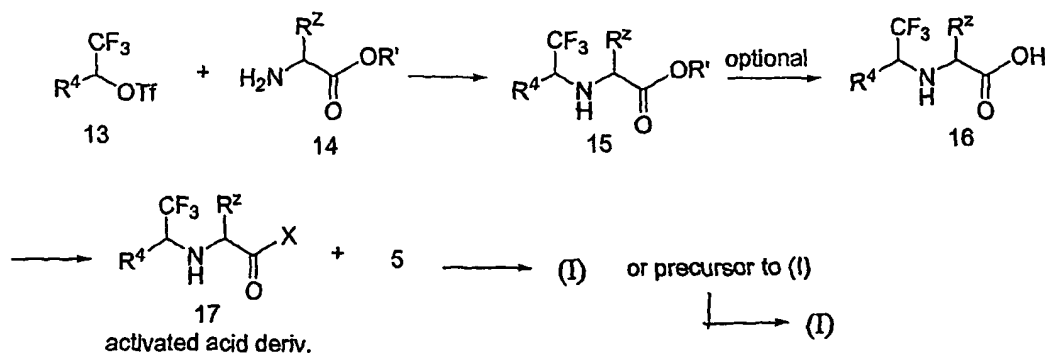
5 \longrightarrow (I)

[0106] Reaction of a compound of formula 2 where R is alkyl and R^3 is as defined in the Summary of the Invention with a hemiacetal compound of formula 6 provides a 2-(1-hydroxy-2,2,2-trifluoroethylamino)acetate compound of formula 11. The reaction is carried out in the presence of a catalytic amount of an acid such as p-toluenesulfonic acid and in an aromatic hydrocarbon solvent such as toluene, benzene, and the like.

[0107] Treatment of 11 with a compound of formula R^4H where R^4 is as defined in the Summary of the Invention under Friedel-Crafts reaction conditions provides a compound of formula 3 which is then converted to a compound of Formula (I) as described above.

15 [0108] Alternatively, the compound of Formula (I) where R^1 , R^2 , R^3 , and R^4 are as defined in the Summary of the Invention and $R^{4'}$ is trifluoromethyl can be prepared as illustrated and described in Scheme 4 below.

Scheme 4



20

[0109] Reaction of a compound of formula 13 where R^4 is as defined in Summary of the Invention with a compound of formula 14 where R' is hydrogen or a carboxy protecting group and R^z is R^3 or a precursor group (e.g., -alkylene-S-trityl or -alkylene-S-alkylene-heteroaryl) to R^3 group provides a compound of formula 15. The reaction is carried out in a
5 suitable organic solvent, including but not limited to, diethyl ether, tetrahydrofuran, acetonitrile, benzene, toluene, xylene, and the like, or mixtures thereof and optionally in the presence of an organic or inorganic base. Preferably, the organic base is triethylamine, pyridine, *N*-methylemorpholine, collidine, diisopropylethylamine, and the like. Preferably, the inorganic base is cesium carbonate, sodium carbonate, sodium bicarbonate, and the like. The
10 reaction is optionally carried out in the presence of a drying agent such as molecular sieves. Preferably, the reaction is carried out at room temperature.

[0110] Compounds of formula 13 can be prepared by methods well known in the art. For example, a compound of formula 13 where R^4 is phenyl or 4-fluorophenyl can be readily prepared from commercially available 2,2,2-trifluoroacetophenone or 2,2,2,4'-
15 tetrafluoroacetophenone respectively, by reducing the keto group to an alcoholic group by suitable reducing agent such as sodium borohydride, lithium aluminum hydride, and the like. The solvent used depends on the type of reducing agent. For example, when sodium borohydride is used the reaction is carried out in an alcoholic organic solvent such as methanol, ethanol, and the like. When lithium aluminum hydride is used the reaction is
20 carried out in an ethereal solvent such as tetrahydrofuran, and the like. Reaction of 2,2,2-trifluoro-1-phenylethanol or 2,2,2-trifluoro-1-(4-fluorophenyl)ethanol with triflic anhydride or trifluoromethanesulfonyl chloride provides the desired compound. Optically enriched compound of formula 15 can be obtained by reduction of the corresponding halogenated acetophenone with a suitable reducing agent such as catecholborane or BH_3 -DMS complex in
25 the presence of a suitable catalyst such as (*S*) or (*R*)-CBS oxazaborolidine catalyst or (*S*) or (*R*)- α,α -diphenyl-2-pyrrolidine-methanol in the presence of BBN to provide chiral alcohol which is then converted to compound 13 as described above. Compounds of formula 14 can be prepared by methods well known in the art.

[0111] Removal of the carboxy protecting group from a compound of formula 15 where R'
30 is a protecting group provides a compound of formula 16. The conditions used to remove the carboxy protecting group depend on the nature of the carboxy protecting group. For example, if R' is alkyl, it is removed under basic hydrolysis reaction conditions utilizing aqueous base such as aqueous lithium hydroxide, sodium hydroxide, and the like in an

alcoholic solvent such as methanol, ethanol, and the like. Additionally, if the R^2 group in compound 14 is a precursor group to R^3 it can be converted to R^3 or to another precursor group to R^3 (e.g., converting -alkylene-S-trityl to -alkylene-S-alkylene-heteroaryl, and the like) prior to proceeding further.

- 5 [0112] Compound 15 (where R' is hydrogen) or 16 is then converted to an activated acid derivative 17 (X is a leaving group) and which upon reaction with an aminoacetonitrile compound of formula 5 provides a compound of Formula (I) when R^2 is R^3 or a precursor compound to (I) when R^2 is a precursor group to R^3 . The activated acid derivative can be prepared and then reacted with compound 5 in a stepwise manner or the acid derivative can be generated *in situ* in the presence of compound 5. For example, if the activated acid is acid halide it is first prepared by reacting 16 with a halogenating agent such as thionyl chloride, oxalyl chloride and the like and then reacted with compound 5. Alternatively, the activated acid derivative is generated *in situ* by reacting compound 16 and 5 in the presence of a suitable coupling agent e.g., benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexyl-carbodiimide (DCC), and the like, optionally in the presence of 1-hydroxybenzotriazole (HOBT), and in the presence of a base such as
- 20 *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like. Suitable reaction solvents are inert organic solvents such as halogenated organic solvents (e.g., methylene chloride, chloroform, and the like), acetonitrile, *N,N*-dimethylformamide, ethereal solvents such as tetrahydrofuran, dioxane, and the like. Alternatively, the activated acid can be reacted with $CR^1R^2(NH_2)CONH_2$ where R^1 and R^2 are as described in the Summary of the
- 25 Invention, followed by conversion of the -CONH₂ group to the cyano group by methods well known in the art. If R^2 is a precursor group to R^3 , it is converted to R^3 group to provide a compound of Formula (I) e.g. conversion of -alkylene-S-alkylene-heteroaryl to -alkylene-SO₂-alkylene-heteroaryl under oxidation reaction conditions.

- [0113] A compound of Formula (I) can be converted to other compounds of Formula (I). For example:

A compound of Formula (I) containing a hydroxy group may be prepared by de-alkylation/benzylation of an alkoxy/benzyloxy substituent; those containing an acid group, by hydrolysis of an ester group; and those containing a cyano, by displacement of a bromine

atom on the corresponding compounds of Formula (I). A compound of Formula (I) containing a halo group such as chloro can be converted to a corresponding compound of Formula (I) containing an methylthio by treating it with sodium thiomethoxide. The methylthio group can be oxidized to methylsulfonyl using a suitable oxidizing agent such as OXONE[®]. A compound of Formula (I) containing a cyano group can be converted to a corresponding carboxy containing compound by hydrolysis of the cyano group. The carboxy group, in turn, can be converted to an ester group.

[0114] A compound of Formula (I) can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula (I) can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula (I) are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of Formula (I) can be prepared using salts of the starting materials or intermediates.

[0115] The free acid or free base forms of the compounds of Formula (I) can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula (I) in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of Formula (I) in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

[0116] The *N*-oxides of compounds of Formula (I) can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula (I) with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula (I) can be prepared from the *N*-oxide of an appropriate starting material.

[0117] Compounds of Formula (I) in unoxidized form can be prepared from *N*-oxides of compounds of Formula (I) by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous
5 dioxane, or the like) at 0 to 80°C.

[0118] Prodrug derivatives of the compounds of Formula (I) can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate
10 prodrugs can be prepared by reacting a non-derivatized compound of Formula (I) with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

[0119] Protected derivatives of the compounds of Formula (I) can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W.
15 Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

[0120] Compounds of the present invention may be conveniently prepared or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0121] Compounds of Formula (I) can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula (I), dissociable complexes are preferred
25 (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent,
30 by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic

mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

Preparation of Biological Agents

[0122] In practicing this invention several processes for the generation or purification of biological agents are used. Methods for preparing the biologics are well known in the art as discussed below.

[0123] Monoclonal antibodies are prepared using standard techniques, well known in the art, such as by the method of Kohler and Milstein, *Nature* 1975, 256:495, or a modification thereof, such as described by Buck *et al.* 1982, *In Vitro* 18:377. Typically, a mouse or rat is immunized with the MenB PS derivative conjugated to a protein carrier, boosted and the spleen (and optionally several large lymph nodes) removed and dissociated into single cells. If desired, the spleen cells may be screened (after removal of non-specifically adherent cells) by applying a cell suspension to a plate or well coated with the antigen. B-cells, expressing membrane-bound immunoglobulin specific for the antigen, will bind to the plate, and will not be rinsed away with the rest of the suspension. Resulting B-cells, or all dissociated spleen cells, are then induced to fuse with myeloma cells to form hybridomas. Representative murine myeloma lines for use in the hybridizations include those available from the American Type Culture Collection (ATCC).

[0124] Chimeric antibodies composed of human and non-human amino acid sequences may be formed from the mouse monoclonal antibody molecules to reduce their immunogenicity in humans (Winter *et al.* *Nature* 1991 349:293; Lobuglio *et al.* *Proc. Nat. Acad. Sci. USA* 1989 86:4220; Shaw *et al.* *J. Immunol.* 1987 138:4534; and Brown *et al.* *Cancer Res.* 1987 47:3577; Riechmann *et al.* *Nature* 1988 332:323; Verhoeven *et al.* *Science* 1988 239:1534; and Jones *et al.* *Nature* 1986 321:522; EP Publication No.519,596, published Dec. 23, 1992; and U.K. Patent Publication No. GB 2,276,169, published Sep. 21, 1994).

[0125] Antibody molecule fragments, e.g., F(ab')₂, FV, and sFv molecules, that are capable of exhibiting immunological binding properties of the parent monoclonal antibody molecule can be produced using known techniques. Inbar *et al.* *Proc. Nat. Acad. Sci. USA* 1972 69:2659; Hochman *et al.* *Biochem.* 1976 15:2706; Ehrlich *et al.* *Biochem.* 1980 19:4091; Huston *et al.* *Proc. Nat. Acad. Sci. USA* 1988 85(16):5879; and U.S. Pat. Nos. 5,091,513 and 5,132,405, and U.S. Pat. No. 4,946,778.

- [0126] In the alternative, a phage-display system can be used to expand the monoclonal antibody molecule populations *in vitro*. Saiki, *et al. Nature* 1986 324:163; Scharf *et al. Science* 1986 233:1076; U.S. Pat. Nos. 4,683,195 and 4,683,202; Yang *et al. J. Mol. Biol.* 1995 254:392; Barbas, III *et al. Methods: Comp. Meth Enzymol.* 1995 8:94; Barbas, III *et al. Proc. Natl. Acad. Sci. USA* 1991 88:7978.
- [0127] The coding sequences for the heavy and light chain portions of the Fab molecules selected from the phage display library can be isolated or synthesized, and cloned into any suitable vector or replicon for expression. Any suitable expression system can be used, including, for example, bacterial, yeast, insect, amphibian and mammalian systems.
- 10 Expression systems in bacteria include those described in Chang *et al. Nature* 1978 275:615, Goeddel *et al. Nature* 1979 281:544, Goeddel *et al. Nucleic Acids Res.* 1980 8:4057, European Application No. EP 36,776, U.S. Pat. No. 4,551,433, deBoer *et al. Proc. Natl. Acad. Sci. USA* 1983 80:21-25, and Siebenlist *et al. Cell* 1980 20:269.
- [0128] Expression systems in yeast include those described in Hinnen *et al. Proc. Natl. Acad. Sci. USA* 1978 75:1929, Ito *et al. J. Bacteriol.* 1983 153:163, Kurtz *et al. Mol. Cell. Biol.* 1986 6:142, Kunze *et al. J. Basic Microbiol.* 1985 25:141, Gleeson *et al. J. Gen. Microbiol.* 1986 132:3459, Roggenkamp *et al. Mol. Gen. Genet.* 1986 202:302, Das *et al. J. Bacteriol.* 1984 158:1165, De Louvencourt *et al. J. Bacteriol.* 1983 154:737, Van den Berg *et al. Bio/Technology* 1990 8:135, Kunze *et al. J. Basic Microbiol.* 1985 25:141, Cregg *et al. Mol. Cell. Biol.* 1985 5:3376, U.S. Pat. Nos. 4,837,148 and 4,929,555, Beach *et al. Nature* 1981 300:706, Davidow *et al. Curr. Genet.* 1985 10:380, Gaillardin *et al. Curr. Genet.* 1985 10:49, Ballance *et al. Biochem. Biophys. Res. Commun.* 1983 112:284-289, Tilburn *et al. Gene* 1983 26:205-221, Yelton *et al. Proc. Natl. Acad. Sci. USA* 1984 81:1470-1474, Kelly *et al. EMBO J.* 1985 4:475479; European Application No. EP 244,234, and International
- 25 Publication No. WO 91/00357.
- [0129] Expression of heterologous genes in insects can be accomplished as described in U.S. Pat. No. 4,745,051, European Application Nos. EP 127,839 and EP 155,476, Vlak *et al. J. Gen. Virol.* 1988 69:765-776, Miller *et al. Ann. Rev. Microbiol.* 1988 42:177, Carbonell *et al. Gene* 1988 73:409, Maeda *et al. Nature* 1985 315:592-594, Lebacqz-Verheyden *et al. Mol. Cell. Biol.* 1988 8:3129, Smith *et al. Proc. Natl. Acad. Sci. USA* 1985 82:8404, Miyajima *et al. Gene* 1987 58:273, and Martin *et al. DNA* 1988 7:99. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts are described in Luckow *et*

al. Bio/Technology 1988 6:47-55, Miller *et al. GENETIC ENGINEERING*, Setlow, J. K. *et al.* eds., Vol. 8, Plenum Publishing, pp. 1986 277-279, and Maeda *et al. Nature* 1985 315:592-594.

[0130] Mammalian expression can be accomplished as described in Dijkema *et al. EMBO J.* 1985 4:761, Gorman *et al. Proc. Natl. Acad. Sci. USA* 1982 79:6777, Boshart *et al. Cell* 1985 41:521, and U.S. Pat. No. 4,399,216. Other features of mammalian expression can be facilitated as described in Ham *et al. Meth. Enz.* 1979 58:44, Barnes *et al. Anal. Biochem.* 1980 102:255, U.S. Pat. Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655 and Reissued U.S. Pat. No. RE 30,985, and in International Publication Nos. WO 90/103430, WO 87/00195.

10 [0131] The production of recombinant adenoviral vectors are described in U.S. Pat. No. 6,485,958.

[0132] Botulinum toxin type A can be obtained by establishing and growing cultures of *Clostridium botulinum* in a fermenter and then harvesting and purifying the fermented mixture in accordance with known procedures.

15 [0133] Any of the above-described protein production methods can be used to provide the biologic that would benefit from the present invention.

Pharmacology and Utility

[0134] The compounds of the invention are selective inhibitors of cysteine proteases such as cathepsin S, K, B, and/or F, and in particular cathepsin S, and accordingly are useful for
20 treating diseases in which cysteine protease activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention are useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, psoriasis, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis, allergic
25 disorders, including, but not limited to, asthma, allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts and endometriosis.

[0135] Cathepsin S is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonitis and cardiovascular disease such as plaque
30 rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

[0136] The cysteine protease inhibitory activities of the compounds of Formula (I) can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known.

Typically, the assay measures protease-induced hydrolysis of a peptide-based substrate.

- 5 Details of assays for measuring protease inhibitory activity are set forth in Biological Examples 1-5, *infra*.

Administration and Pharmaceutical Compositions

[0137] In general, compounds of Formula (I) will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or

- 10 in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula (I) may range from about 10 micrograms per kilogram body weight ($\mu\text{g/kg}$) per day to about 100 milligram per kilogram body weight
- 15 (mg/kg) per day, typically from about 100 $\mu\text{g/kg/day}$ to about 10 mg/kg/day. Therefore, a therapeutically effective amount for an 80 kg human patient may range from about 1 mg/day to about 8 g/day, typically from about 1 mg/day to about 800 mg/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of
- 20 Formula (I) for treating a given disease.

[0138] The compounds of Formula (I) can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions,

- 25 suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula (I) in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is
- 30 generally available to one of skill in the art.

[0139] Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate,

glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

[0140] The amount of a compound of Formula (I) in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula (I) for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula (I) are described in Example 1 below.

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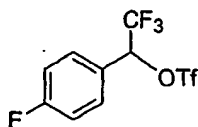
Examples

[0141] The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula (I) (Examples) and intermediates (References) according to the invention.

20

Reference A

Synthesis of trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl ester



25 Step 1

[0142] To a stirred solution of 2,2,2,4'-tetrafluoroacetophenone (10 g, 52.1 mmol) in methanol (50 mL) was added NaBH₄ (0.98 g, 26.5 mmol) at 0°C. After stirring at 25°C for 2 h, the reaction mixture was quenched by adding 1N HCl (100 mL) and then extracted with ethyl ether. The ether extract was washed with brine, dried with MgSO₄, and concentrated to

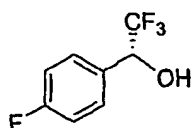
give 2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (11.32 g) which was used in next step without further purification.

Step 2

[0143] NaH (640 mg, 16mmol, 60% in mineral oil) was washed twice with hexane (20 mL) and then suspended in dried diethyl ether (20 mL). A solution of 2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (1.94 g, 10 mmol) in diethyl ether (10 mL) was added at 0° C. After stirring for 2 h at room temperature, a solution of trifluoromethanesulfonyl chloride (1.68 g, 10 mmol) in diethyl ether (10 mL) was added. After 2 h, the reaction mixture was quenched by adding a solution of sat NaHCO₃ and the product was extracted with diethyl ether. The extracts were washed with brine and dried, and the solvent was removed to yield trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl ester (3.3 g).

Reference B

Synthesis of 2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethanol

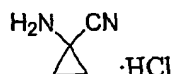


[0144] To a -78 °C toluene (25 mL)/dichloromethane (25 mL) solution of 2,2,2,4'-tetrafluoroacetophenone (2.5 g, 13.01 mmol) and 1M *S*-methyl CBS oxazaborolidine catalyst (1.3 mL, 1.3 mmol) was added freshly distilled catecholborane (1.66 mL, 15.62 mmol). The reaction mixture was maintained at -78 °C for 16 h at which time 4N HCl (5 mL in dioxane) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate and washed with a saturated brine solution. The organic layer was dried over magnesium sulfate, filtered and concentrated to provide a solid. The solid was suspended in hexanes and filtered off. The hexanes filtrate containing the desired product was concentrated and the residue subjected to flash chromatography (hexanes:ethylacetate 1:10) to provide the title compound as a colorless oil (2.2g, 87% yield). The ratio of enantiomers was determined to be 95:5 by chiral HPLC (Chiralcel OD column, 95 hexanes: 5 isopropanol mobile phase. Ret. time of the major product was 6.757 min. Ret. Time for the minor isomer was 8.274 min.).

[0145] 2,2,2-Trifluoro-1(*S*)-(4-fluorophenyl)ethanol can be prepared by using *R*-methyl CBS oxazaborolidine.

Reference C

5 Synthesis of 1-aminocyclopropanecarbonitrile hydrochloride



10 Step 1

[0146] A mixture of benzophenone imine (25 g, 0.138 mol, Aldrich) and aminoacetonitrile hydrochloride (25 g, 0.270 mol, Lancaster) in dichloromethane (1000 mL) was stirred in a 2L Erlenmeyer flask under nitrogen at room temperature for 5 days. The reaction mixture was filtered to remove the precipitated ammonium chloride and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was dissolved in ether (400 mL) washed with water (200 mL) and brine. After drying over magnesium sulfate the solution was evaporated to give (benzhydrylideneamino)-acetonitrile (47.89 g).

Step 2

[0147] A solution of sodium hydroxide (91 g, 2.275 mol) in water (91 mL) in a 2L flask was cooled on ice under nitrogen and then treated with benzyl triethyl ammonium chloride (2.0 g, 0.0088 mol, Aldrich) and (benzhydrylideneamino)acetonitrile (47.89 g) in toluene (100 mL).

[0148] 1,2-Dibromoethane (23 mL, 122.4 mmol, Aldrich) was then added dropwise over 25 min, to the reaction mixture with mechanical stirring and cooling to maintain the internal temperature near +10 °C. The reaction mixture was then stirred vigorously for 24 h at room temperature and then poured into ice water and extracted with toluene. The combined extracts were washed with brine and then treated with MgSO₄ and Norite. After filtering, toluene was removed by rotary evaporation to give an oil (67 g). The residue was dissolved in boiling hexane (400 mL), treated with Norite and filtered hot and allowed to cool. A dark oil separated which was removed by pipette (~2 mL). Scratching induced crystallization in the remaining solution which was cooled on ice for 2 h. Light yellow crystals were collected

by filtration and washed with cold hexane to give 1-(benzhydrylideneamino)cyclopropanecarbonitrile (30.56 g).

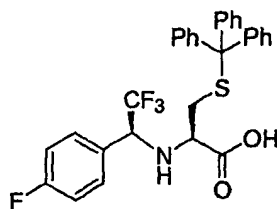
Step 3

- [0149] A mixture of 1-(benzhydrylideneamino)cyclopropanecarbonitrile (30.56 g, 0.124 mol) in concentrated HCl (12 mL) in water (100 mL) and ether (100 mL) was stirred at room temperature for 15 h. The ether layer was discarded and the aqueous layer was washed with ether. The aqueous layer was then freeze dried to give the title compound as a tan powder (13.51 g). This compound is also commercially available.

10

Reference D

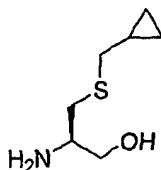
Synthesis of 2(R)-[2,2,2-trifluoro-1(S)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid



15

- [0150] To a slurry of S-trityl-L-cysteine (4.86 g, 13.37 mmol) in dichloromethane (97 mL, 20 mL/g AA) at room temperature was added diisopropylethylamine (9.32 mL, 53.48 mmol) followed by a solution of trifluoromethanesulfonic acid 2,2,2-trifluoro-1(RS)-phenylethyl ester (5.32 g, 16.04 mmol) (major enantiomer (S), 90 ee) in dichloromethane (15 mL) via syringe all at once. After 19 h, the reaction mixture was concentrated on the rotovap to give an oil. Diethyl ether was added and the solution was washed with 1N HCl and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. Flash chromatography of the residue with 2 hexanes/1 ethyl acetate/.25% acetic acid as the eluent provided 2(R)-[2,2,2-trifluoro-1(S)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid (6 g) (major diastereomer (R,S), 90 de) as an oil/foam.

Reference E

Synthesis of 2(*R*)-amino-3-cyclopropylmethylsulfanylpropan-1-ol

Step 1

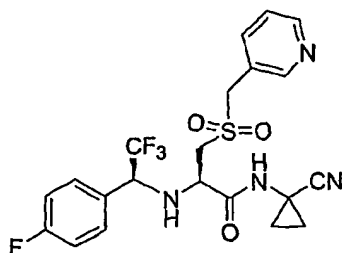
- 5 [0151] An ice water bath cooled solution of L-cysteine in 1N sodium hydroxide (740 mL) and dioxane (740 mL) was treated with bromomethylcyclopropane (50 g, 370 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Dioxane was removed under reduced pressure and the resulting aqueous solution was adjusted to pH 6 with 6N HCl and placed in a refrigerator for 20 h. The product was collected by vacuum
10 filtration, washed with hexanes and lyophilized to give 2(*R*)-amino-3-cyclopropylmethylsulfanylpropionic acid (57.28 g) as a white solid.

Step 2

- [0152] To an ice water cooled solution of lithium aluminum hydride (200 mL of 1.0 M) was added solid 2(*R*)-amino-3-cyclopropylmethylsulfanylpropionic acid. The addition was
15 done by tapping in portions through a funnel in such a manner as to control hydrogen gas evolution. The ice bath was removed, and the reaction mixture was heated at reflux for 16 h. The reaction mixture was removed from heat and cooled in an ice water bath. Diethyl ether (110 mL) was added, followed by dropwise addition of water (5 mL), 15% aqueous sodium hydroxide (5 mL), and water (15 mL). After stirring in the ice water bath for 1.5 h, the
20 reaction mixture was filtered. The filtrate was dried over anhydrous sodium sulfate, and concentrated to give 2(*R*)-amino-3-cyclopropylmethylsulfanyl-propan-1-ol (14.9 g).

Example 1

Synthesis of *N*-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
(compound 2)



Step 1

[0153] To a solution of 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-trityl-sulfanylpropionic acid (539 mg, 1 mmol, 90% de), prepared as described above, in CH₂Cl₂ was added trifluoroacetic acid (0.4 mL, 4 mmol) and triethylsilane (0.4 mL, 2mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed up to room temperature and stirred for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in 1N NaOH (12 mL). The aqueous layer was washed with hexane and to the basic solution was added dioxane (12 mL), P(CH₂CH₂COOH)₃.HCl (28 mg, 0.1 mmol) and 3-chloromethyl-pyridine (196 mg, 1.2 mmol) and the reaction mixture was stirred at room temperature 2h. The dioxane was removed under reduced pressure and residue was acidified with 6N HCl to pH 5. The product was extracted with ethyl acetate and after drying the organic extracts with MgSO₄, the solvent was removed to give 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethyl-amino]-3-(pyridin-3-ylmethylsulfanyl)propionic acid which was used in the next step without further purification.

Step 2

[0154] 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethylsulfanyl)-propionic acid was dissolved in DMF (5 mL) and 1-aminocyclopropanecarbonitrile (142 mg, 1.2 mmol), HATU (456 mg, 1.2 mmol) and NMM (0.44 mL, 4 mmol) were added. After stirring for 2 h at rt, saturated NH₄Cl and ethyl acetate were added and stirring was continued for 20 min. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with MgSO₄ and the solvent was removed under the reduced pressure to give *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-

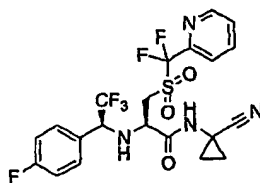
1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethylsulfanyl)propionamide as an oil. The crude was used in the next step without further purification.

Step 3

[0155] *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethylsulfanyl)propionamide was dissolved in MeOH (3 mL) and OXONE[®] (460 mg, 1.5 mmol) in H₂O (3 mL) was added. After stirring at rt for 2 h, the solvent was removed and the residue was extracted with ethyl acetate. The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure. The title compound was purified by Prep-HPLC.

Example 2

Synthesis of *N*-(1-cyanocyclopropyl)-3-(difluoropyridin-2-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide
(compound 23)



Step 1

[0156] To a solution of (Boc-Cys-OH)₂ (20 g, 45.4 mmol) and P(CH₂CH₂COOH)₃.HCl (15.61 g, 54.47 mmol) in DMF (162 mL) was added 5N KOH (109 mL) slowly over 20 min. After stirring overnight, 2-picolylchloride hydrochloride (22.34 g, 136.2 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 2.5h. The pH of the solution was adjusted to 3 with 10N HCl and the product was extracted with methylene chloride. The combined organic extract was washed with sat. NaHCO₃, dried over MgSO₄, filtered and concentrated to give 2(*R*)-*N*-*tert*-butoxycarbonylamino-3-(pyridin-2-ylmethylsulfanyl)propionic acid which was crystallized from methylene chloride and hexane mixture to give pure product (13.70 g) as a white solid.

Step 2

[0157] 2(*R*)-*N*-*tert*-Butoxycarbonylamino-3-(pyridin-2-ylmethylsulfanyl)propionic acid (3.12 g, 10 mmol) was dissolved in mixture of methanol (10 mL) and benzene (10 mL).

Trimethylsilyl-diazomethane (10 mL, 2.0M solution in hexane, 20 mM) was added slowly. After 1 h, the solvent was removed to give methyl 2(R)-*N*-*tert*-butoxycarbonylamino-3-(pyridin-2-ylmethyl-sulfanyl)-propionate as a yellow oil.

Step 3

- 5 [0158] Methyl 2(R)-*N*-*tert*-butoxycarbonylamino-3-(pyridin-2-ylmethylsulfanyl)-propionate was dissolved in dioxane and 3 equiv. of 4M HCl in dioxane was added. After stirring at room temperature for 3 h, the solvent was removed under reduced pressure to give methyl 2(R)-amino-3-(pyridin-2-ylmethylsulfanyl)propionate hydrochloride as a hygroscopic solid.

10 Step 4

- [0159] To a mixture of methyl 2(R)-amino-3-(pyridin-2-ylmethylsulfanyl)propionate hydrochloride (1.31 g, 5 mmol), 2,2,2-trifluoro-1-(4-fluorophenyl)ethanone (0.875 g), DIPEA (2.39 g, 18.5 mmol), in dichloromethane (20 mL) was added titanium tetrachloride (4.65 mmol) dropwise over 5 min. After stirring for 3 h at ambient temperature, additional titanium
15 tetrachloride (0.3 mmol) was added. After an additional hour of stirring, NaCNBH₄ (0.973 g, 15.5 mmol) was added in methanol (10 mL). After 1 h, the reaction mixture was diluted with ethyl acetate (200 mL) and poured onto magnesium sulfate. After filtration and concentration, the residue was purified by flash chromatography to afford methyl 3-(pyridin-2-yl-methylsulfanyl)-2(R)-[2,2,2-trifluoro-1(RS)-(4-fluorophenyl)ethylamino]-propionate
20 (640 mg, 1.59 mmol).

Step 5

- [0160] To a solution of methyl 3-(pyridin-2-ylmethylsulfanyl)-2(R)-[2,2,2-trifluoro-1(RS)-(4-fluorophenyl)ethylamino]propionate (0.64 g, 1.59 mmol) in methanol (9 mL) was added 1N sodium hydroxide (4.77 mL). The resulting solution was stirred for 2 h at ambient
25 temperature and then methanol was removed *in vacuo*. The residue was portioned between water and ethyl acetate. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were dried over magnesium sulfate. Removal of the solvents provided 3-(pyridin-2-ylmethylsulfanyl)-2(R)-[2,2,2-trifluoro-1(RS)-(4-fluorophenyl)ethylamino]propionic acid (0.410 g, 1.06 mmol) as a white solid which was a
30 mixture of diastereomers.

[0161] 3-(Pyridin-2-ylmethylsulfanyl)-2(R)-[2,2,2-trifluoro-1(RS)-(4-fluorophenyl)ethylamino]-propionic acid was converted to of *N*-(1-cyanocyclopropyl)-3-

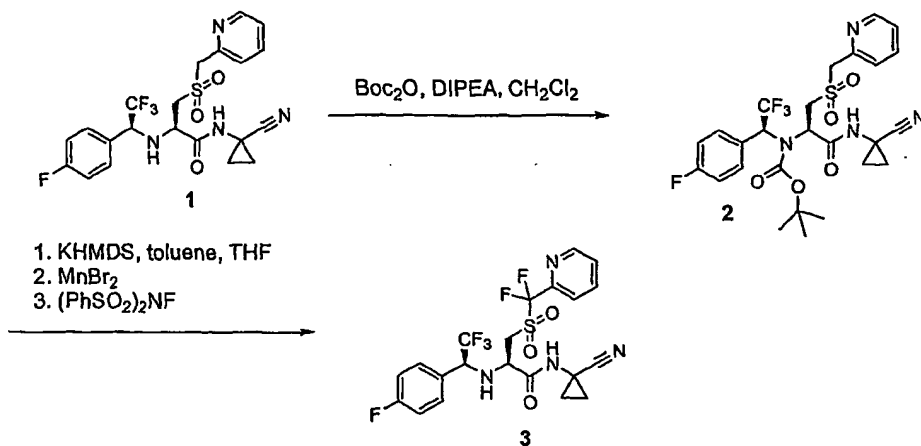
(pyridin-2-ylmethylsulfanyl)-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]propionamide by proceeding as described in Example 1, Step 2 above. *N*-(1-Cyanocyclopropyl)-3-pyridin-2-ylmethanesulfanyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (95 mg) was obtained from the diastereomeric mixture
5 by flash chromatography and was converted to *N*-(1-cyano-cyclopropyl)-3-pyridin-2-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethyl-amino)propionamide compound (50 mg) by proceeding as described in Example 1, Step 3 above.

Step 6

[0162] To *N*-(1-cyanocyclopropyl)-3-pyridin-2-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (0.200 g, 0.412 mmol) in dichloromethane (5 mL) was added DIPEA (0.058 g, 4.53 mmol) and the slight suspension cooled in an ice-water bath. Boc-anhydride (0.099 mg, 0.453 mmol) was added in one portion and the resulting opaque solution was allowed to warm to ambient temperature overnight. The reaction was diluted to 100 mL with EtOAc and the organic phase extracted once with 10 mL 0.1 N HCl,
15 sodium bicarbonate, and brine and dried over MgSO₄. Removal of solvent afforded [1(*R*)-(1-cyanocyclopropyl-carbamoyl)-2-(pyridin-2-ylmethanesulfonyl)ethyl]-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethyl]carbamic acid *tert*-butyl ester (0.200 g) as a white solid, which was used without further purification.

Step 7

[0163] To a 0.5M solution of potassium bis(trimethylsilyl)amide (1.02 mmol) in toluene, cooled to -78 °C, was added [1(*R*)-(1-cyanocyclopropylcarbamoyl)-2-(pyridin-2-ylmethanesulfonyl)-ethyl]-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethyl]carbamic acid *tert*-butyl ester (0.2 g, 0.34 mmol) in THF (2 mL) and the brown solution was stirred for 40 min at -78 °C. MnBr₂ was added as a solid, in one portion, resulting in a brown suspension. After
25 stirring for 30 min, (PhSO₂)₂NF (0.304 g, 0.964 mmol) was added as a solid and the reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to ambient temperature overnight. After partitioning between 0.5 N HCl and EtOAc the organic phase was extracted with bicarbonate, brine, and dried over MgSO₄. The crude residue was purified via flash chromatography with EtOAc/hexanes (0 to 40% EtOAc gradient) affording the title
30 compound. MS : 519.2, (M - 1) 543.1 (M + 23). Also, *N*-(1-cyanocyclopropyl)-3-(fluoropyridin-2-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide was isolated as a diastereomeric mixture.

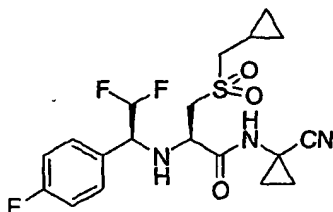


Example 3

Synthesis of *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2-difluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

5

(compound 48)



Step 1

- 10 [0164] A solution of 2(*R*)-amino-3-cyclopropylmethylsulfanylpropan-1-ol (4.9 g, 30.4 mmol), difluoroacetaldehyde ethyl hemiacetal (4.6 g, 36.5 mmol), and PPTS (415 mg) in toluene (100 mL) was heated at reflux with Dean Stark trapping of water for 4 h. After cooling to ambient temperature, the solution was filtered through a pad of silica gel and concentrated to an oil. The oil was further purified via silica gel chromatography with
- 15 1:1(v/v) hexanes: diethyl ether as the elution solvent. Concentration of the appropriate fractions yielded a diastereomeric mixture of 4-cyclopropylmethylsulfanyl-methyl-2-difluoromethyloxazolidine (4.2 g) as a clear oil.

Part A:

- [0165] A solution of 4-cyclopropylmethylsulfanyl-methyl-2-difluoromethyloxazolidine (2.08 g, 9.3 mmol) in anhydrous THF (25 mL) was cooled in an ice/water bath and treated
- 20 with chlorotrimethylsilane (1.2 g, 1.4 mL) and lithium bis(trimethylsilyl)amide (11.2 mL of a

1.0 M solution in tetrahydrofuran). The reaction mixture was allowed to stir under ice bath cooling for 30 min and then slowly heated to 60° C for 1 h to ensure complete equilibration to the *E* imine isomer. The reaction mixture containing (2-cyclopropylmethylsulfanyl-1-trimethylsilanyloxy-methylethyl)-(2,2-difluoroethylidene)amine was allowed to cool to room temperature.

Part B:

[0166] A solution of 4-fluorobromobenzene (4.9 g, 27.9 mmol) in anhydrous tetrahydrofuran (55 mL) was cooled to -78° C, treated with *n*-butyllithium (11.15 mL of 2.5 M solution in hexanes) and allowed to stir for 15 min. The solution from Part A was transferred by syringe to this reaction mixture at -78° C over 10 min. Stirring at -78° C for 2 h was followed by addition of aq 2.5 N HCl (10 mL), then the reaction mixture was allowed to warm to room temperature and stirred at room temperature for 30 min. Potassium hydroxide (9 mL of 25% solution in water) was added and the reaction mixture was extracted 2 times with 100 mL portions of diethyl ether. The combined organic layers were dried over MgSO₄, concentrated, and chromatographed using 20% ethyl acetate: 80% hexanes (v/v) as the elution solvent. Concentration of the appropriate fractions yielded 3-cyclopropylmethylsulfanyl-2(*R*)-[2,2-difluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propan-1-ol (1.45 g) as a clear oil.

Step 3

[0167] A stock solution of H₅IO₆/CrO₃ was prepared as described in *Tet. Lett.* 1998 39(30) pp. 5323-5326. This was done by dissolving H₅IO₆ (11.4 g, 50 mmol) and CrO₃ (56 mg, 2.4 mol %) in anhydrous acetonitrile (115 mL) and stirred overnight. The next morning 855 µL of water was added to the stock solution and stirred for an additional 10 min. H₅IO₆/CrO₃ (53 mL) of the stock solution was chilled to 0° with stirring, and a solution of 3-cyclopropylmethylsulfanyl-2(*R*)-[2,2-difluoro-1(*S*)-(4-fluorophenyl)ethylamino]propan-1-ol (1.45 g) in acetonitrile (25 mL) was added dropwise so as to maintain the reaction temperature at 0° C. After 4 h, isopropanol (50 mL) was added. The reaction mixture was allowed to warm to room temperature and then was concentrated. The resulting solids were partitioned between ethyl acetate and saturated aqueous KH₂PO₄. The aqueous layer was dried over anhydrous MgSO₄. Removal of solvent gave 3-cyclopropylmethylsulfonyl-2(*R*)-[2,2-difluoro-1(*S*)-(4-fluoro-phenyl)ethylamino]-propionic acid (0.95 g).

Step 4

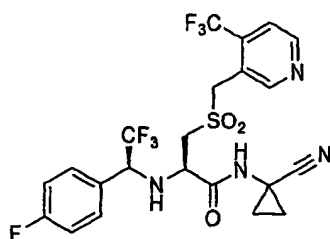
[0168] To a solution of 3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,-difluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propionic acid (0.95 g), 1-aminocyclopropanecarbonitrile HCl salt (400 mg) in DMF (5 mL) at room temperature was added HATU (1.28 g), followed by diisopropylethylamine (1.68 g/ 2.26 mL). After being stirred at room temperature for 4
 5 hours, the reaction mixture was concentrated under reduced pressure and then partitioned between ethyl acetate and brine. The combined organic extracts were dried over anhydrous MgSO₄ and concentrated under reduced pressure, and the residue was purified by recrystallization from 2-propanol to yield *N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2-[2,2-difluoro-1-(4-fluorophenyl)ethylamino]-propionamide as
 10 colorless crystals (250 mg).

[0169] ¹H NMR sample acquired in d₆-dimethylsulfoxide is referenced to residual CD₃SOCD₂H at 2.49 ppm. ¹H NMR (400 MHz): δ 8.97 (s, 1H), 7.4-7.35 (m, 2H), 7.21-7.16 (m, 2H), 6.09 (dt, 1H), 3.98 (m, 1H), 3.53 (m, 1H), 3.40 (m, 1H), 3.26-3.20 (m, 2H), 3.17-3.11 (m, 2H), 1.38 (m, 2H), 1.08 (m, 1H), 0.99 (m, 1H), 0.80 (m, 1H), 0.6 (m, 2H), 0.38 (m,
 15 2H)

[0170] ¹³C NMR Sample acquired in d₆-dimethylsulfoxide is referenced to residual ¹³CD₃SOCD₃ at 39.5 ppm. ¹³C NMR (125 MHz): δ 172.16, 163.04, 161.09, 132.12, 130.66, 130.59, 120.37, 118.24, 116.31, 115.28, 115.11, 114.37, 62.11, 61.94, 61.76, 58.58, 55.12, 54.38, 19.53, 15.49, 15.45, 3.95, 3.82, 3.78. Exact Mass for C₁₉H₂₂F₃N₃O₃S = 429.1.
 20 Electrospray HPLC/MS M+H = 430.1, M-H = 428.2

Example 4

Synthesis of *N*-(1-cyanocyclopropyl)-3-(4-(trifluoromethyl)pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide
 25 (compound 1)



Step 1

[0171] 4-Trifluoromethylnicotinic acid (2 g, 10.4 mmol) was dissolved in THF and BH_3 -THF 1.0M complex (50 mL, 50 mmol) was added at room temperature under N_2 . The reaction mixture was stirred at room temperature overnight. 6N HCl was added slowly to
5 quench the reaction. Solvent was removed under reduced pressure and the aqueous layer was adjusted to pH 5 and extracted with ethyl acetate. The combined organic layers were dried with MgSO_4 , filtered and concentrated under the reduced pressure. The crude (4-trifluoromethylpyridin-3-yl)methanol was dissolved in CH_2Cl_2 and SOCl_2 (2.2 mL, 30 mmol) was added at room temperature. The reaction mixture was stirred at room temperature
10 overnight. The solvent was removed under the reduced pressure and the crude 3-chloromethyl-4-trifluoromethylpyridine was used without further purification.

Step 2

[0172] Catecholborane (19.4 mL, 182 mmol) in dichloromethane 15 mL) was added to a dichloromethane solution of *S*-methyl CBS oxazaborolidine (13 mL, 13 mmol) and 2,2,2,4'-tetrafluoroacetophene (18.2 mL, 130.13mmol) dropwise at -78°C in 30 min and stirred at -78°C overnight. The reaction mixture was quenched by addition of 4N HCl in dioxane (13 mL) at -78°C , warmed up to room temperature and the solvent was removed under reduced pressure. 10% NaHSO_3 solution (200 mL) was added and the aqueous layer was extracted with hexane. The organic layer was washed with water and dried with MgSO_4 . The solvent
20 was removed under reduced pressure to give 2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (20 g) as colorless oil (90% d.e.).

Step 3

[0173] NaH (11.87 g, 296.7 mmol) was added to Et_2O (700 mL) at 0°C under N_2 and a solution of 2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (44.3 g, 228.2 mmol) in ether was
25 added at 0°C under N_2 . The reaction mixture was stirred 10 min at 0°C then 1 h at room temperature. Trifluoromethanesulfonyl chloride (50 g, 296.7 mmol) in Et_2O was added at 0°C under N_2 and the reaction mixture was stirred 10 min at 0°C and then 3 h at room temperature. The solvent was removed under the reduced pressure and H_2O (100 mL) was added slowly. The aqueous layer was extracted by hexane and the combined organic layer
30 was dried with MgSO_4 . The solvent was removed under the reduced pressure to give trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl ester (70 g, 90% d.e) as colorless oil.

Step 4

[0174] 2-Amino-3-tritylsulfanylpropionic acid (78 g, 214.6 mmol) was dissolved in CH₂Cl₂, DIPEA (112 mL, 643.8mmol) was added and the reaction mixture was stirred for 10 min at room temperature. Trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl ester (70 g, 214.6 mmol) in CH₂Cl₂ was added and the reaction mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure, the residue was dissolved in Et₂O and the solution was washed with 1N HCl, brine, and dried with MgSO₄. Solvent was removed to give a mixture of 2(R)-[2,2,2-trifluoro-1(S)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid and 2(R)-[2,2,2-trifluoro-1(R)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid (90 g, 90% de) as yellow solid.

Step 5

[0175] A mixture of 2(R)-[2,2,2-trifluoro-1(S)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid and 2(R)-[2,2,2-trifluoro-1(R)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid (5.4 g, 10 mmol) was dissolved in CH₂Cl₂, TFA (3.1 mL, 40 mmol) and Et₃SiH (3.2 mL, 20mmol) were added at 0 °C under N₂. The reaction mixture was warmed up to room temperature and stirred for 2 h. Solvent was removed under reduced pressure and the residue was dissolved in 120 mL of 1N NaOH. The aqueous layer was washed with hexane and used in the next step without further purification. To the aqueous solution was added dioxane (120 mL), 3-chloromethyl-4-trifluoromethylpyridine (1.95 g, 10 mmol), and tris(2-carboxyethyl)phosphine hydrochloride (280 mg, 1mmol). The reaction mixture was stirred at room temperature overnight. Dioxane was removed under the reduced pressure. The aqueous solution was adjusted to pH 3 and was extracted with ethyl acetate. The combined organic layer was dried with MgSO₄ and removed under the reduced pressure. The crude product 2(R)-[2,2,2-trifluoro-1(S)-(4-fluorophenyl)ethylamino]-3-(4-trifluoromethylpyridin-3-ylmethylsulfanyl)-propionic acid containing minor amounts of other diastereomer was used in the next step without further purification.

Step 6

[0176] 2(R)-[2,2,2-Trifluoro-1(S)-(4-fluorophenyl)ethylamino]-3-(4-trifluoromethylpyridin-3-ylmethylsulfanyl)-propionic acid, 1-aminocyclopropanecarbonitrile hydrochloride (1.18 g, 10 mmol), HATU (4.56g, 12 mmol), and NMM (4.4 mL, 40 mmol) were added to DMF and the reaction mixture stirred at room temperature for 2 h. Sat. NH₄Cl (10 mL) and ethyl acetate (10 mL) were added and stirring was continued for 20 min at room temperature. The aqueous layer was extracted with ethyl acetate. The combined organic layer

was washed with brine and dried over MgSO₄. Solvent was removed under reduced pressure and crude product *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-3-(4-trifluoromethyl-pyridin-3-ylmethylsulfanyl)propionamide was used in the next step without further purification.

5 Step 7

[0177] *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(4-trifluoromethyl-pyridin-3-ylmethylsulfanyl)-propionamide was dissolved in CH₃OH (10 mL) and an aqueous solution of Oxone[®] (3 g in 10 mL H₂O, 10 mmol) was added. The reaction mixture was stirred at room temperature 3 h. Solvent was removed under the reduced
10 pressure. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine and dried with MgSO₄. The solvent was removed under the reduced pressure and the crude product was purified by prep-HPLC to isolate the title compound from the diastereomeric mixture.

[0178] ¹H-NMR(DMSO-d₆): δ 0.83(m, 1H), 1.07(m, 1H), 1.39(m, 2H), 3.74(m, 2H),
15 3.83(b, 1H), 4.43(m, 1H), 4.98(q, 2H), 7.27(t, 2H), 7.49(t, 2H), 7.87(d, 1H), 8.86(s, 1H), 8.89(d, 1H), 9.18(s, 1H). LC-MS: 553(M+1), 551, (M-1), 575(M+23).

[0179] The following compounds were prepared by the procedure described in Example 4 above using appropriated starting materials.

[0180] *N*-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide. (compound 2), LC-MS: 485(M+1), 507(M+23),
20 483(M-1).

[0181] *N*-(1-cyanocyclopropyl)-3-(pyridazin-3-ylmethanesulfonyl)-2-(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 3), MS (486.2 M+1, 483.9 M-1).

25 [0182] *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylfuran-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide, Compound 4, ¹H-NMR: (CDCl₃): 7.47(1H, s, NH), 7.33-7.29(2H, m), 7.24(1H, s), 7.07-7.02(2H, m), 6.79-6.77(1H, m), 6.60-6.55(1H, d), 4.59-4.4(2H, ab), 4.25-4.23(1H, m), 3.64-3.55(1H, m), 3.53-3.48(1H, dd), 3.27-3.21(1H, dd), 3-2.9(1H, m), 1.5-1.4(2H, m), 1.13-1.07(2H, m).

30 [0183] LC-MS: 540.2(M-1), 542.3(M+1), 564.1(M+Na).

[0184] *N*-(1-cyanocyclopropyl)-3-(2-methylthiazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide, Compound 6, ¹H-NMR: (CDCl₃): 7.41(1H, s, NH), 7.31-7.27(2H, m), 7.06-7.01(2H, m), 4.6-4.3(2H, dd), 4.3-4.23(1H, m), 3.7-3.64(1H, m), 3.63-3.55(1H, dd), 3.38-3.3(1H, aa), 3.2-3.1(1H, m), 2.65(3H, s), 1.55-1.45(2H, m), 1.23-1.1(2H, m). LC-MS: 503(M-1), 504.8(M+1), 526.9(M+Na).

[0185] *N*-(1-cyanocyclopropyl)-3-pyridin-4-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide.. (compound 7), LC-MS: 485(M+1), 483(M-1).

[0186] *N*-(1-cyanocyclopropyl)-3-(pyrimidin-4-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 8), MS (486.2 M+1, 484.0 M-1).

[0187] *N*-(1-cyanocyclopropyl)-3-[2-(1-oxopyrrol-1-yl)ethanesulfonyl]-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide. (compound 9), LC-MS: 501.3(M-1), 503.0(M+1), 525.2(M+Na).

[0188] *N*-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*R*)-4-fluorophenylethylamino)propionamide. (compound 10), LC-MS: 485(M+1), 507(M+23), 483(M-1).

[0189] *N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(3-fluorophenyl)ethylamino]propionamide (compound 11) was repared by replacing 2,2,2,4'-tetrafluoroacetophenone with commercial 2,2,2,3'-tetrafluoroacetophenone and following the procedures of Reference B, Reference A, step 2, and Example 4 above, by replacing trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl ester with trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(3-fluorophenyl)-ethyl ester and 3-chloromethyl-4-trifluoromethylpyridine with cyclopropylmethylbromide. MW = 447.45 ; MS(+1) = 448.0 ; MS(-1) = 446.2 ; MS(+Na) = 470.0.

[0190] *N*-(1-cyanocyclopropyl)-3-(3,3,3-trifluoropropane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide. (compound 12), LC-MS: 490(M+1), 512(M+23), 488(M-1).

[0191] *N*-(1-cyanocyclopropyl)-3-(4-1H-[1.2.4]triazol-1-ylphenylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 14), MS (551.2 M+1, 549.4 M-1).

- [0192] *N*-(1-cyanocyclopropyl)-3-[2-(2-oxo-2,3-dihydrobenzimidazol-1-yl)ethanesulfonyl]-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide. (compound 15), LC-MS: 554(*M*+1), 576(*M*+23), 552(*M*-1).
- 5 [0193] *N*-(1-cyanocyclopropyl)-3-(5-oxo-pyrrolidin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylaminopropionamide. (compound 16), LC-MS: 491(*M*+1), 513(*M*+23), 489(*M*-1).
- [0194] *N*-(1-cyanocyclopropyl)-3-(2-fluoropyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylaminopropionamide. (compound 17), LC-MS: 503(*M*+1), 525(*M*+23), 501(*M*-1).
- 10 [0195] *N*-(1-cyanocyclopropyl)-3-(quinolin-2-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 25), MS (535.2 *M*+1, 533.2 *M*-1).
- [0196] *N*-(1-cyanocyclopropyl)-3-(2,6-difluorophenylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 31), MS (520.2 *M*+1,
- 15 518.1 *M*-1).
- [0197] *N*-(1-cyanocyclopropyl)-3-(2,4-difluorophenylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 32), MS (520.6 *M*+1, 518.2 *M*-1).
- [0198] *N*-(1-cyanocyclopropyl)-3-(quinolin-3-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-
- 20 1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 33), MS (535.1 *M*+1, 533.3 *M*-1).
- [0199] *N*-(1-cyanocyclopropyl)-3-(4,4,4-trifluorobutane-1-sulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 34) MW = 503.44 ; MS(+1) = 504.1 ; MS(-1) = 502.1 ; MS(+Na) = 526.2. Prepared as described above but replacing 3-chloromethyl-4-trifluoromethylpyridine with commercial 4,4,4-trifluoro-1-bromobutane.
- 25 [0200] *N*-(1-cyanocyclopropyl)-3-(2-pyridin-2-ylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide. (compound 39), LC-MS: 499(*M*+1), 521(*M*+23), 497(*M*-1).

- [0201] *N*-(1-cyanocyclopropyl)-3-(2-pyridin-3-ylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide. (compound 41), LC-MS: 499(*M*+1), 521(*M*+23), 497(*M*-1).
- [0202] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*RS*)-2-chloropyridin-5-ylethylamino)propionamide. (compound 49), LC-MS: 463.2(*M*-1), 465.2(*M*+1), 487.2(*M*+Na).
- [0203] *N*-(1-cyanocyclopropyl)-3-(quinoxalin-2-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 55), MS (536.2 *M*+1, 534.4 *M*-1).
- 10 [0204] *N*-(1-cyanocyclopropyl)-3-(ethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethyl-amino)propionamide. (compound 62), LC/MS data: *M*+ = 421.9; *M*- = 420.1.
- [0205] *N*-(1-cyanocyclopropyl)-3-(methanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide. (compound 68), LC/MS data: *M*+ = 408.1; *M*- = 15 406.2.
- [0206] *N*-(1-cyanocyclopropyl)-3-(propane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethyl-amino)propionamide (compound 69), LC/MS data *M*+ = 435.8; *M*- = 434.3.
- [0207] *N*-(1-cyanocyclopropyl)-3-(1*H*-indol-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide; (compound 70), LC-MS: 523(*M*+1), 545(*M*+23), 521(*M*-1).
- 20 [0208] *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,4-difluorophenylethylamino)propionamide; (compound 73), LC-MS: 503(*M*+1), 525(*M*+23), 501(*M*-1).
- [0209] *N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,4-difluorophenylethylamino)propionamide; (compound 74), LC-MS: 503(*M*+1), 525(*M*+23), 501(*M*-1).
- 25 [0210] *N*-(1-cyanocyclopropyl)-3-[2-(1*H*-indol-3-yl)ethanesulfonyl]-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 75), MS (537.4 *M*+1, 535.2 *M*-1).
- 30 1).

[0211] The heteroarylmethyl halide was either commercially available or prepared as follows:

Synthesis of 5-chloromethylpyrimidine.

[0212] 5-Methylpyrimidine (3.0 g, 31.9 mmol), *N*-chlorosuccinamide (5.23 g, 39.2 mmol), and benzoyl peroxide (0.077 g, 0.319 mmol) were combined in carbon tetrachloride (100 mL). The suspension was heated for 7 h at reflux. The reaction was cooled, filtered, concentrated and finally purified via flash chromatography with ethyl acetate/hexanes as eluent.

[0213] *N*-(1-cyanocyclopropyl)-3-(tetrahydro-pyran-4-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)-ethylamino]-propionamide. (compound 76), MW = 491.51 ; MS(+1) = 492.3 ; MS(-1) = 490.1 ; MS(+Na) = 514.3.

[0214] Prepared as described above by replacing 3-chloromethyl-4-trifluoromethylpyridine with 4-iodomethyltetrahydropyran prepared as described below.

[0215] A solution of (tetrahydropyran-4-yl)methanol (0.5 g), triethylamine (1.2 mL) and dichloromethane (15 mL) was cooled to -40 °C and treated with methanesulfonylchloride (333 uL). The reaction mixture was allowed to stir at -40 °C to -20 °C for 2. It was then diluted with 25 mL dichloromethane, washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated. Acetone (40 mL) and sodium iodide (1.3 g) were added and the reaction mixture was heated at reflux for 16 h. The reaction mixture was diluted with dichloromethane and filtered. The filtrate was concentrated to provide 4-iodomethyltetrahydro-pyran which was used without further purification.

[0216] *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1-(3-hydroxy-6-methyl-pyridin-2-yl)-ethylamino]-propionamide. (compound 85)

[0217] MW = 460.48 ; MS(+1) = 461.1, MS(-1) = 459.0, MS(+Na) = 483.1 was prepared by replacing trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(*RS*)-phenylethyl ester with trifluoro-methanesulfonic acid 2,2,2-trifluoro-1-(3-hydroxy-6-methyl-pyridin-2-yl)-ethyl ester prepared as described below.

[0218] 6-Methyl-2-(2,2,2-trifluoro-1-hydroxy-ethyl)-pyridin-3-ol was prepared by a modification of a procedure detailed in *J. Heterocyclic Chem.*, 38, 25 (2001), p 25 by replacing traditional heating with microwave heating as follows.

Step 1

[0219] A mixture of commercially available 6-methylpyridin-3-ol (500 mg), trifluoroacetaldehyde methylhemiacetal (715 mg) and potassium carbonate (69 mg) was heated in a microwave reactor at 180 °C for 3 min. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography using 1:1 hexane:ethyl acetate and recrystallized from ethyl acetate and hexane to give 627 mg of 6-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-ol.

10 Step 2

[0220] 6-Methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-3-ol was converted to trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(3-hydroxy-6-methyl-pyridin-2-yl)-ethyl ester by the method described in step 2 of reference A.

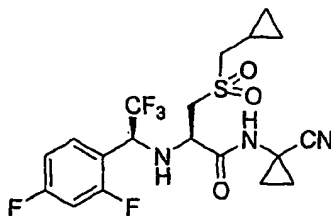
[0221] *N*-(1-cyanocyclopropyl)-3-(2-*tert*-butyl-[1.3.4]-thiadiazol-5-ylmethanesulfonyl)-2-(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (compound 86), LC-MS: 546.1(*M*-1), 548.1(*M*+1), 569.8(*M*+Na).

[0222] *N*-(1-cyanocyclopropyl)-3-(2,4,6-trifluorophenylmethanesulfonyl)-2-(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide. (compound 87), MS (538.2 *M*+1, 536.1 *M*-1).

20

Example 5

Synthesis of *N*-(1-cyanocyclopropyl)-2-(*R*)-[2,2,2-trifluoro-1(*S*)-(2,4-difluoro-phenyl)ethyl-amino]-3-(cyclopropylmethylsulfonyl)propionamide (compound 43)



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Step 1

[0223] 2,4-Difluorobenzaldehyde (1.1 mL, 10.0 mmol) and (trifluoromethyl)trimethylsilane (1.77 mL, 12.0 mmol) were dissolved in THF (25 mL) and

then cooled to 0 °C. To this, 1M TBAF in THF (76 µL, 76 µmol) was added and the reaction mixture was allowed to warm to room temperature. After 3.25 h, 2.5M HCl (25 mL) was added. The reaction was stirred for 1 h and then extracted with ether. The organic layer was washed with brine and dried with Na₂SO₄. The solvent was removed under the reduced
5 pressure to give 2,2,2-trifluoro-1-(2,4-difluoro-phenyl)ethanol (2.5 g) as a racemic mixture.

Step 2

[0224] 2,2,2-Trifluoro-1-(2,4-difluorophenyl)ethanol (1.36 g, 6.4 mmol) was dissolved in dichloromethane (25 mL) and diisopropylethylamine (DIPEA, 5 mL, 28.8 mmol) was added. The resulting solution was cooled to -78 °C and trifluoromethanesulfonic anhydride (1.81 g,
10 6.4 mmol) was added. After 1 h, the reaction was warmed to -15 °C stirring was continued for 2 h. S-trityl-L-cysteine (2.33 g, 6.4 mmol) was then added and the reaction mixture was stirred overnight. After an aqueous work-up, the organic layer was dried with MgSO₄ then filtered through silica using a combination of ethyl acetate and acetic acid to give a diastereomeric mixture of 2(R)-[1-(2,4-difluorophenyl)-2,2,2-trifluoroethylamino]-3-
15 tritylsulfanylpropionic acid (2.47 g).

Step 3

[0225] 2(R)-[1-(2,4-Difluorophenyl)-2,2,2-trifluoroethylamino]-3-tritylsulfanylpropionic acid (2.47 g, 4.4 mmol) was dissolved in a 30% TFA / 30 % Et₃SiH / 40 % CH₂Cl₂ v/v/v solution (5 mL). After stirring for 1 h, toluene was added and all solvents were removed
20 under reduced pressure. A basic aqueous work-up was done using 2.7 M NaOH. To the aqueous layer, P(CH₂CH₂COOH)₃ hydrochloride (126 mg, 0.44 mmol) and cyclopropylmethyl bromide (427 µL, 4.4 mmol) were added. After stirring overnight, an acidic aqueous work-up was done. The organic layer was washed with brine and dried with MgSO₄. The solvent was removed to get a diastereomeric mixture of 3-
25 cyclopropylmethylsulfanyl-2(R)-[1-(2,4-difluorophenyl)-2,2,2-trifluoroethylamino]propionic acid (1.25 g).

Step 4

[0226] 3-Cyclopropylmethylsulfanyl-2(R)-[1-(2,4-difluorophenyl)-2,2,2-trifluoroethylamino]-propionic acid (1.25 g, 3.4 mmol), HATU (1.29 g, 3.4 mmol), DIPEA
30 (1.48 mL, 8.5 mmol) and 1-amino-cyclopropanecarbonitrile hydrochloride (403 mg, 3.4 mmol) was dissolved in NMP (20 mL). After stirring overnight, Oxone™ (3.14 g, 5.1 mmol) dissolved in water (7.9 mL) was added. After 1 h, more Oxone™ (3.14 g, 5.1 mmol)

was added and the reaction mixture was stirred overnight. The product was precipitated from solution by the addition of water. The precipitate was purified by C18 RP-HPLC using an 0.1 mM HCl and acetonitrile system to give a diastereomeric mixture of *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*R*)-(2,4-difluoro-phenyl)ethylamino]-3-

- 5 (cyclopropylmethylsulfonyl)propionamide and *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(2,4-difluorophenyl)ethylamino]-3-(cyclopropylmethylsulfonyl)-propionamide (~250 mg).

[0227] Approximately 50 mg of the diastereomeric mixture was then purified on a Chiralcel OD-H (2 cm X 25 cm) HPLC column using a mixture of IPA and hexanes and the
10 diastereomeric mixture was separated.

[0228] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,4-difluorophenylethylamino)propionamide. LC-MS: 466 (*M*+1), 464 (*M*-1), 488 (*M*+23). ¹H-NMR(CDCl₃): 7.50 (s, 1H), 7.43 (q, 1H), 6.99 (m, 1H), 6.90 (m, 1H), 4.65 (q, 1H), 3.71(dd, *J*= 5.56, 4.95 Hz, 1H), 3.59 (dd, *J*=14.55, 6.05 Hz, 1H), 3.35 (dd, *J*=14.56, 4.50 Hz,
15 1H), 3.03(d, 2H), 1.18 (m, 4H), 0.77 (m, 2H), 0.45 (m, 2H).

[0229] Following the procedure described in Example 5 above, the following compounds were prepared using the appropriated fluorinated benzaldehyde starting materials.

[0230] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,5-difluorophenylethylamino)propionamide, (compound 37). LC-MS: 466 (*M*+H),
20 488 (*M*+Na), 464 (*M*-H), 444 (*M*-HF).

[0231] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,5-difluorophenylethylamino)propionamide, (compound 38). LC-MS: 466 (*M*+H), 488 (*M*+Na), 464 (*M*-H), 444 (*M*-HF).

[0232] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,3-difluorophenylethylamino)propionamide, (compound 42). LC-MS: 466 (*M*+H), 488 (*M*+Na), 464 (*M*-H), 444 (*M*-HF).
25

[0233] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,5-difluorophenylethylamino)propionamide, (compound 63). LC-MS: 466 (*M*+H), 488 (*M*+Na), 464 (*M*-H), 444 (*M*-HF).

- [0234] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,6-difluorophenylethylamino)propionamide, (compound 64). LC-MS: 466 (*M*+*H*), 488 (*M*+*Na*), 464 (*M*-*H*), 444 (*M*-*HF*).
- 5 [0235] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,6-difluorophenylethylamino)propionamide, (compound 65). LC-MS: 466 (*M*+*H*), 488 (*M*+*Na*), 464 (*M*-*H*), 444 (*M*-*HF*).
- [0236] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,3-difluorophenylethylamino)propionamide, (compound 66). LC-MS: 466 (*M*+*H*), 488 (*M*+*Na*), 464 (*M*-*H*), 444 (*M*-*HF*).
- 10 [0237] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,4-difluorophenylethylamino)propionamide (compound 67). LC-MS: 466 (*M*+1), 464 (*M*-1), 488 (*M*+23). ¹H-NMR(CDCl₃): 7.83 (s, 1H), 7.52 (q, 1H), 7.00 (m, 1H), 6.90 (m, 1H), 4.42 (m, 1H), 3.68(m, 1H), 3.42 (m, 1H), 3.28 (m, 1H), 2.89 (d, 2H), 1.28 (m, 4H), 0.75 (m, 2H), 0.41 (m, 2H).
- 15 [0238] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide, (compound 71). LC-MS: 448 (*M*+*H*), 470 (*M*+*Na*), 446 (*M*-*H*), 426 (*M*-*HF*).
- [0239] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-fluorophenylethylamino)propionamide, (compound 72). LC-MS: 448 (*M*+*H*), 470
- 20 (*M*+*Na*), 446 (*M*-*H*), 426 (*M*-*HF*).
- [0240] *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide, (compound 77). LC-MS: 501 (*M*+*H*), 523 (*M*+*Na*), 499 (*M*-*H*), 479 (*M*-*HF*). This compound was isolated as by-product in the preparation of that gave the corresponding pyridine derivative.
- 25 [0241] *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-fluorophenylethylamino)propionamide, (compound 78). LC-MS: 501 (*M*+*H*), 523 (*M*+*Na*), 499 (*M*-*H*), 479 (*M*-*HF*). This compound was isolated as by-product in the preparation of that gave the corresponding pyridine derivative.

[0242] *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-fluorophenylethylamino)propionamide, (compound 79). LC-MS: 485 (*M*+*H*), 507 (*M*+*Na*), 483 (*M*-*H*), 463 (*M*-*HF*).

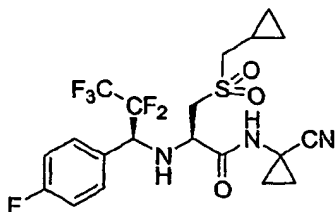
[0243] *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-fluorophenylethylamino)propionamide, (compound 80). LC-MS: 485 (*M*+*H*), 507 (*M*+*Na*), 483 (*M*-*H*), 463 (*M*-*HF*).

[0244] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,3,4-trifluorophenylethylamino)propionamide, (compound 81). LC-MS: 484 (*M*+*H*), 506 (*M*+*Na*), 482 (*M*-*H*), 462 (*M*-*HF*).

[0245] *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,3,4-trifluorophenylethylamino)propionamide, (compound 82). LC-MS: 484 (*M*+*H*), 506 (*M*+*Na*), 482 (*M*-*H*), 462 (*M*-*HF*).

Example 6

Synthesis of *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-[2,2,3,3,3-pentafluoro-1(*S*)-(4-fluorophenyl)propylamino]propionamide (compound 54)



Step 1

[0246] To a solution of 1-bromo-4-fluorobenzene (16.5 mL, 0.15 mol) in anhydrous THF (200 mL) at -78 °C, 2,2,3,3,3-pentafluoropropionic acid ethyl ether (14.4 g, 75 mmol) was slowly added. After stirring for 4 h at -78 °C, ethyl ether (200 mL) and sat. sol. of NH_4Cl (100 mL) were added. The resulting mixture was placed in a sep. funnel, shaken and the organic phase separated. After washing with brine, the solution was dried over magnesium sulfate. The solution was concentrated in a rotary vapor and the residue was purified by distillation to give 2,2,3,3,3-pentafluoro-1-(4-fluorophenyl)propan-1-one.

Step 2

[0247] To a solution of 2,2,3,3,3-pentafluoro-1-(4-fluorophenyl)propan-1-one (13.0 g, 53 mmol) in a mixture 1:1 of dichloromethane and toluene (160 mL) at room temperature, 1M solution of *S*-methyl-CBS-oxazaborolidine in toluene (5.3 mL, 5.3 mmol) was added at room temperature. The reaction mixture was cooled at -78 °C and catecholborane (7.62 g, 63 mmol) was added. After stirring for 7 h at -78 °C, a 4 M solution of HCl in dioxane (18 mL) was added. After allowing the reaction mixture to warm to room temperature, water (5 mL) was added, stirred for 5 min and 10% solution of sodium metabisulfite (25 mL) was added. The heterogeneous mixture was stirred for 15 min and the solid was separated by filtration. The solution was concentrated on rotovap to reduce the amount of dichloromethane and then the residue was diluted with hexanes (100 mL). The resulting solution was washed with a 10% solution of sodium metabisulfite (100 mL) and brine (100 mL). After drying over magnesium sulfate, the solution was concentrated and the crude was purified on a silica gel column, using dichloromethane as eluent to give (*R*)-2,2,3,3,3-pentafluoro-1-(4-fluorophenyl)propan-1-ol as an oil (12.01 g).

Step 3

[0248] A 60% suspension of NaH in oil (2.35 g, 58.8 mmol) was washed several times with hexanes and after suspending it in anhydrous ethyl ether (100 mL), (*R*)-2,2,3,3,3-pentafluoro-1-(4-fluoro-phenyl)propan-1-ol (12.0 g, 49 mmol) in ether (20 mL) was added slowly at room temperature. After stirring for 15 min, the reaction mixture was cooled at 0 °C and trifluoromethylsulfonyl chloride (12.38 g, 73.7 mmol) was added. The reaction mixture was stirred for 1:30 h at 0 °C, then concentrated under reduced pressure and the residue was diluted with hexane (100 mL). The reaction mixture was washed with sat. sol. NaHCO₃, brine and dried over magnesium sulfate. After removing the solvent on rotovapor, trifluoromethanesulfonic acid (*R*)-2,2,3,3,3-pentafluoro-1-(4-fluorophenyl)propyl ester was obtained as a colorless oil (16.0 g).

Step 4

[0249] To a suspension of L-trityl-cysteine (15.45 g, 42 mmol) and diisopropyl ethyl amine (29.3 mL, 168 mmol) in dichloromethane (350 mL), a solution of trifluoromethanesulfonic acid (*R*)-2,2,3,3,3-pentafluoro-1-(4-fluorophenyl)-propyl ester (16.0 g, 42 mmol) in dichloromethane (20 mL) was added at room temperature. The reaction mixture was stirred for 20 h and then concentrated. The residue was dissolved in ethyl acetate (300 mL). The organic phase was washed with cold 1N HCl (100 mL), brine and dried over magnesium

sulfate. After solvent evaporation, the crude was purified by flash chromatography, using a mixture 1:2 of EA/hexanes to give 2(*R*)-[2,2,3,3,3-pentafluoro-1-(*S*)-(4-fluorophenyl)propylamino]-3-tritylsulfanyl-propionic acid as an oil (6.93 g).

Step 5

- 5 [0250] To a solution of 2(*R*)-[2,2,3,3,3-pentafluoro-1-(*S*)-(4-fluorophenyl)propylamino]-3-tritylsulfanylpropionic acid (6.92 g, 12 mmol) in dichloromethane (10 mL), triethylsilane (3.73 mL, 23.4 mmol) and TFA (3.61 mL, 46.9 mmol) were added at room temperature. The reaction mixture was stirred for 4 h. The solvent and volatiles were evaporated on rotovap, benzene was added to the residue and the mixture was evaporated again to ensure complete
10 removal of excess TFA. The residue was dissolved in 1 N NaOH (50 mL) and extracted with hexanes. To the resulting solution, P(CH₂CH₂CO₂H)₃.HCl (0.343 g, 1.2 mmol) was added, and a 0.2 M stock solution of 2(*R*)-[2,2,3,3,3-pentafluoro-1-(*S*)-(4-fluorophenyl)propylamino]-3-mercaptopropionic acid was obtained.

Step 6

- 15 [0251] To a 0.2 M stock solution of 2(*R*)-[2,2,3,3,3-pentafluoro-1-(*S*)-(4-fluorophenyl)propyl-amino]-3-mercaptopropionic acid in NaOH (10 mL, 2 mmol), cyclopropylmethylbromide (0.270 g, 2 mmol) was added. After stirring the reaction mixture for 5 h at room temperature, 1 M HCl solution was added until pH 2-3. The reaction mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine
20 and dried over sodium sulfate and concentrated to give 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,3,3,3-pentafluoro-1-(*S*)-(4-fluoro-phenyl)propylamino]-propionic acid as a foam (0.678 g).

Step 7

- [0252] To a solution of 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,3,3,3-pentafluoro-1-(*S*)-(4-fluoro-phenyl)propylamino]-propionic acid (0.670 g, 1.67 mmol) in DMF (3 mL), 1-amino-cyclopropanecarbonitrile hydrogen chloride salt (0.236 g, 3 mmol), HATU (0.760 g, 2 mmol) and diisopropyl ethyl amine (0.87 mL, 5 mmol) were added. After stirring for 4 h, the reaction mixture was diluted with ethyl acetate (20 mL) and then washed with a sat. solution of NaHCO₃ (10 mL), water (10 mL) and brine (10 mL). The crude solution was dried over
25 sodium sulfate. After evaporation of the solvent, the crude oil was purified by flash chromatography, using a mixture 1:1 of EA/Hexanes to give *N*-(1-cyanocyclopropyl)-3-
30

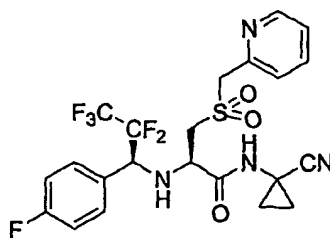
(cyclopropylmethanesulfanyl)-2(*R*)-(3,3,3,2,2-pentafluoro-1(*S*)-4-fluorophenylpropylamino)propionamide as a light yellow solid (0.558 g).

Step 8

[0253] To a solution of *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfanyl)-2(*R*)-(3,3,3,2,2-pentafluoro-1(*S*)-4-fluorophenylpropylamino)propionamide (0.540 g, 1.16 mmol) in *N*-methylpyrrolidinone (4 mL), a solution of OXONE (1.06 g, 1.74 mmol) in water (3.8 mL) was added at room temperature. The heterogeneous mixture was stirred overnight at room temperature. After cooling at 0 °C, water (20 mL) was added and mixture was stirred for 15 min. The solid was separated by filtration and washed with fresh water. The crude solid was purified by flash chromatography using a mixture of EA/H as eluent to give title compound as a white solid (0.105 g, 19%). ¹H NMR (DMSO-*d*₆): δ 8.94 (1H, s), 7.44 (2H, dd), 7.22 (2H, t), 4.53 (1H, m), 3.68 (1H, q), 3.66 (1H, m), 3.30 (2H, m), 3.12 (2H, m), 1.30 (2H, m), 1.00 (1H, m), 0.90 (1H, m), 0.58 (2H, m), 0.47 (1H, m), 0.30 (2H, m). LC/MS, M+1: 498.4, M-1: 496.3.

Example 7

Synthesis of *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-[2,2,3,3,3-pentafluoro-1(*S*)-(4-fluorophenyl)propylamino]propionamide (compound 50)



Step 1

[0254] To a 0.2 M stock solution of 3-mercapto-2(*R*)-[2,2,3,3,3-pentafluoro-1(*S*)-(4-fluorophenyl)propylamino]-propionic acid in NaOH (10 mL, 2 mmol), 2-chloromethylpyridine (0.328 g, 2 mmol) and 1 N solution of NaOH (1 mL) were added. After stirring the reaction mixture for 5 h at room temperature, 1 M HCl solution was added until pH 5-6. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine and dried over sodium sulfate and concentrated to give *N*-(1-

cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfanyl)-2(*R*)-[3,3,3,2,2-pentafluoro-1(*S*)-(4-fluorophenyl)propylamino]-propionamide as a foam (0.692 g) which was converted to the title compound as described in Example 6 above.

[0255] ¹H NMR (DMSO-*d*₆): δ 8.97 (1H, s), 8.60 (1H, m), 7.88 (1H, m), 7.47 (4H, m), 7.24 (2H, t), 4.74 (2H, s), 4.58 (1H, m), 3.73 (2H, m), 3.44 (2H, m), 1.33 (2H, m), 0.93 (1H, m), 0.53 (1H, m). LC/MS, M+1: 535.3; M-1: 533.4 and compound 51 (15 %) as a by-product.. LC/MS, M+1: 551.3, M-1: 549.4.

[0256] Proceeding as described in Example 7 above but substituting 2-chloromethylpyridine with 3-chloromethylpyridine provided *N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(3,3,3,2,2-pentafluoro-1(*S*)-4-fluorophenylpropylamino)-propionamide (compound 52), ¹H NMR (DMSO-*d*₆): δ 9.00 (1H, s), 8.61 (1H, m), 8.57 (1H, m), 7.80 (1H, m), 7.48 (3H, m), 7.24 (2H, t), 4.64 (2H, dd), 4.58 (1H, m), 3.82 (1H, t), 3.70 (1H, m), 3.42 (1H, m), 3.30 (1H, m), 1.20 (2H, m), 0.90 (1H, m), 0.50 (1H, m). LC/MS, M+1: 535.3, M-1: 533.2. Compound 53 was obtained as a by-product (5%). LC/MS, M+1: 551.3, M-1: 549.3; and

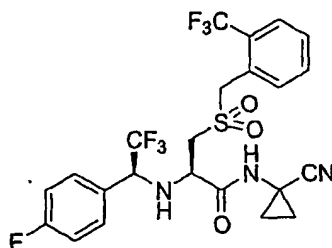
[0257] *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-3-ylmethanesulfonyl)-2(*R*)-(3,3,3,2,2-pentafluoro-1(*S*)-4-fluorophenylpropylamino)-propionamide (compound 53)

[0258] Proceeding as described in Example 7 above but substituting 2-chloromethylpyridine with 5-methylisoxazol-3-ylmethyl chloride provide *N*-(1-cyanocyclopropyl)-3-(5-methylisoxazol-3-ylmethanesulfonyl)-2(*R*)-(3,3,3,2,2-pentafluoro-1(*S*)-4-fluorophenylpropylamino)-propionamide (compound 59), ¹H NMR (DMSO-*d*₆): 8.97(1H, s), 7.46 (2H, dd), 7.24 (2H, dd), 6.32 (1H, s), 4.74 (2H, d), 4.55 (1H, m), 3.70 (2H, m), 3.44 (2H, m), 2.45 (3H, s), 1.33 (2H, m), 0.92 (1H, m), 0.52 (1H, m). LC/MS: M-1: 536.9, M+1: 539.2

[0259] Proceeding as described in Example 7 *N*-(1-cyanocyclopropyl)-3-(2-pyridin-2-ylethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-fluorophenylethylamino)propionamide was prepared (compound 88), ¹H NMR (DMSO-*d*₆): 8.97(1H, s), 8.75(1H, d), 8.28(1H, m), 7.82(1H, d), 7.72(1H, m), 7.46 (2H, dd), 7.24 (2H, dd), 4.74 (1H, m), 4.00-3.30(7H, bm), 1.33 (2H, m), 0.92 (1H, m), 0.52 (1H, m). LC/MS: M-1: 547.5, M+1: 549.3

Example 8

Synthesis of *N*-(1-cyanocyclopropyl)-3-(2-(trifluoromethyl)phenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide
(compound 35)



- [0260] 2-(Trifluoromethyl)benzyl bromide (0.50 mmol) was dissolved in dioxane (3 mL) and a 0.16 M stock solution of 3-mercapto-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionic acid (4.7 mL, 0.75 mmol) in 1.0 M aqueous sodium hydroxide/0.032 M tris(2-carboxyethyl)phosphine hydrochloride was added. After stirring overnight, the reaction mixture was concentrated to half the volume and then diluted with water and washed with heptane. Ethyl acetate (5 mL) was added and the two phase mixture was placed in an ice/water bath and the pH was adjusted to 3 with 3.0 M hydrochloric acid. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. The residue was dissolved in DMF (2 mL) and 1-aminocyclopropanecarbonitrile hydrochloride (64 mg, 0.54 mmol), DIPEA (260 μL, 1.5 mmol), HATU (191 mg, 0.50 mmol) were added and the reaction mixture was stirred overnight. After concentrating the residue was dissolved in EtOAc and washed with 1.0 M KHSO₄, saturated NaHCO₃, and brine and dried over anhydrous MgSO₄. Solvent was removed and the residue was dissolved in acetonitrile (3 mL) and a 0.50 M aqueous solution of Oxone™ (1.5 mL, 0.75 mmol) was added. After stirring overnight, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel to give the title compound (55 mg) as a white solid mixture of diastereomers in 80% de (1*S*,2*R*) > (1*R*,2*R*). (compound 35), LC-MS: 552(M+1), 551(M-1), 574(M+23), H-NMR(DMSO): 0.80(m, 1H), 1.05(m, 1H), 1.38(m, 2H), 3.38(m, 1H), 3.68(m, 2H), 3.80(m, 1H), 4.40(m, 1H), 4.88(q, 2H), 7.25(t, 2H), 7.47(dd, 2H), 7.65(m, 2H), 7.75(m, 1H), 7.82(d, 1H), 9.10(s, 1H).
- [0261] Following the procedure described above the following compounds were prepared.

[0262] *N*-(1-cyanocyclopropyl)-3-(2-methylpropylsulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (compound 29), LC-MS: 450(*M*+1), 448(*M*-1), 472(*M*+23).

[0263] *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethoxyphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide (compound 36), LC-MS: 568(*M*+1), 566(*M*-1), 590(*M*+23).

[0264] *N*-(1-cyanocyclopropyl)-3-(tetrahydropyran-2*RS*-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide (compound 56),

[0265] LC-MS: 492(*M*+1), 490(*M*-1), 514(*M*+23).

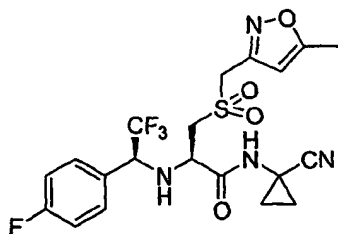
[0266] *N*-(1-cyanocyclopropyl)-3-(2,6-dichlorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (compound 57), LC-MS: 552:554:556 ratio 9:6:1(*M*+1); 550, 552, 554 ratio 9:6:1(*M*-1); 574, 576, 578 ratio 9:6:1(*M*+23).

[0267] *N*-(1-cyanocyclopropyl)-3-(1-ethyl-2,5-dioxopyrrolidin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide (compound 89)

[0268] LC-MS: 553(*M*+1), 551(*M*-1), 575(*M*+23).

Example 9

Synthesis of *N*-(1-cyanocyclopropyl)-3-(5-methylisoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide (compound 28)



[0269] 3-(Bromomethyl)-5-methylisoxazole (0.5 mmol) was dissolved in acetonitrile (1.5 mL) and a 0.50 M stock solution of 3-mercapto-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethyl-amino]propionic acid (1.5 mL, 0.75 mmol) in 2.0 M aqueous sodium

- hydroxide was added. After 2 h, water (2 mL) and acetonitrile (2 mL) were added and the two phase mixture was washed with heptane. The heptane extract was discarded and the aqueous phase was placed in an ice/water bath and the pH was adjusted to 3 with 1.0 M aqueous KHSO₄. The organic phase was separated and the aqueous phase was extracted with
- 5 EtOAc. The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and concentrated. The residue was dissolved in acetonitrile (3 mL) and 1-aminocyclopropanecarbonitrile hydrochloride (88 mg, 0.74 mmol), DIPEA (390 μ L, 2.2 mmol) and HATU (287 mg, 0.75 mmol) were added. After 2 h, the reaction mixture was diluted with and a 0.50 M aqueous solution of Oxone™ (3.0 mL, 1.5 mmol) was added.
- 10 After stirring the reaction mixture at 50° for 2 h, water (5 mL) was added and the reaction mixture was concentrated to remove acetonitrile. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with 1.0 M aqueous KHSO₄, 1:1 water:saturated NaHCO₃, and brine, and dried over anhydrous MgSO₄. After concentration, the residue through a plug of silica gel using EtOAc eluent and collected all material with R_f
- 15 > 0.5. After concentration the residue was purified by flash chromatography to give title compound (63 mg) as a white solid mixture of diastereomers, 85% de, (1'S,2R) > (1'R,2R). LC-MS: 489(M+1), 487(M-1), 511(M+23). H-NMR(DMSO): 0.74(m, 1H), 1.01(m, 1H), 1.36(m, 2H), 2.44(s, 3H), 3.36(m, 1H), 3.68(m, 2H), 3.75(m, 1H), 4.41(m, 1H), 4.77(q, 2H), 6.33(s, 1H), 7.25(t, 2H), 7.47(dd, 2H), 9.04(s, 1H).
- 20 [0270] Following the procedure described above, the following compounds were prepared:
- [0271] *N*-(1-cyanocyclopropyl)-3-(benzo[1.2.5]thiadiazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide (compound 26), LC-MS: 542(M+1), 540(M-1), 564(M+23).
- [0272] *N*-(1-cyanocyclopropyl)-3-(benzothiazol-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (compound 27), LC-MS: 541(M+1), 539(M-
- 25 1), 563(M+23).
- [0273] *N*-(1-cyanocyclopropyl)-3-(cyclobutylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (compound 30), LC-MS: 462(M+1), 460(M-1), 484(M+23).
- 30 [0274] *N*-(1-cyanocyclopropyl)-3-(quinolin-8-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide (compound 41), LC-MS: 535(M+1), 533(M-1), 557(M+23).

[0275] *N*-(1-cyanocyclopropyl)-3-(5-methyl-3-phenylisoxazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide (compound 44),

[0276] LC-MS: 565(*M*+1), 563(*M*-1), 587(*M*+23).

5 *N*-(1-cyanocyclopropyl)-3-(4-methyl-2-phenyl-[1.2.3]triazol-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)-propionamide (compound 45), LC-MS: 565(*M*+1), 563 (*M*-1), 487(*M*+23).

[0277] *N*-(1-cyanocyclopropyl)-3-(2-cyanophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide (compound 46), LC-MS: 509(*M*+1), 507(*M*-1), 531(*M*+23).

10 [0278] *N*-(1-cyanocyclopropyl)-3-(3-methoxycarbonylphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide (compound 47),

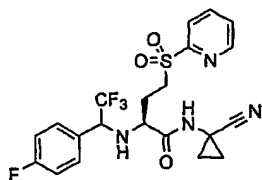
[0279] LC-MS: 542(*M*+1), 540(*M*-1), 4564(*M*+23).

[0280] *N*-(1-cyanocyclopropyl)-3-(3-methoxycarbonylfuran-2*RS*-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide (compound 58),

15 [0281] LC-MS: 532(*M*+1), 530(*M*-1), 554(*M*+23).

Example 10

Synthesis of *N*-(1-cyanocyclopropyl)-2(*S*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]-4-(pyridin-2-ylsulfonyl)butyramide



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Step 1

[0282] 3(*S*)-Aminodihydrofuran-2-one (12.4 g, 68.2 mmol) was added in dioxane (136 mL) and 1*N* NaOH (136 mL) was added to give a clear solution. The reaction mixture was cooled in ice-water bath and Boc-anhydride (16.35 g, 74.9 mmol) was added in portions. The reaction mixture was warmed to ambient temp. overnight and after concentrating it to approx. 150 mL, ethyl acetate (150 mL) was added. After acidifying the reaction mixture to pH 4 with concentrated aqueous KHSO₄, the organic layer was separated and concentrated to give (2-

25

oxotetrahydro-furan-3(*R*)-yl)-carbamic acid *tert*-butyl ester as a white solid which was used without further purification.

Step 2

[0283] Clean sodium metal (0.205 g, 8.95 mmol) was added, in portions, to anhydrous methanol (20 mL) in a thick walled tube. The suspension was stirred under anhydrous nitrogen until all the metal had dissolved, then pyridine-2-thiol (1.0 g, 8.95 mmol) was added. After stirring for 20 min, (2-oxotetrahydro-furan-3(*R*)-yl)-carbamic acid *tert*-butyl ester (1.8 g, 8.95 mmol) was added as a solid and the tube was capped and heated to 100 °C for 16 h. The reaction mixture was concentrated, then purified via flash chromatography (MeOH, CH₂Cl₂ as eluent) to give 2(*S*)-*tert*-butoxycarbonylamino-4-(pyridin-2-ylsulfanyl)butyric acid (0.75 g) as a clear oil.

Step 3

[0284] To 2(*S*)-*tert*-butoxycarbonylamino-4-(pyridin-2-ylsulfanyl)butyric acid (0.75 g, 2.40 mmol) in methanol (16 mL) and toluene (50 mL) was added a 2.0M solution of (trimethylsilyl)diazomethane (3.12 mmol) dropwise. After 3 h, the reaction mixture was concentrated to give methyl 2(*S*)-*tert*-butoxycarbonylamino-4-(pyridin-2-ylsulfanyl)butyrate as an oily residue which was used without further purification.

Step 4

[0285] To methyl 2(*S*)-*tert*-butoxycarbonylamino-4-(pyridin-2-ylsulfanyl)butyrate (0.75 g, 2.4 mmol) in THF (5 mL) was added methanesulfonic acid (6.9 g, 7.2 mmol) in one portion. The solution was stirred for 16 h and the crude reaction mixture was concentrated to give methyl 2(*S*)-amino-4-(pyridin-2-ylsulfanyl)butyrate as the mesylate salt which was used directly in the next step.

Step 5

[0286] Methyl 2(*S*)-amino-4-(pyridin-2-ylsulfanyl)butyrate (0.610 g, 2.33 mmol), 2,2,2,4'-tetrafluoroacetophenone (0.393 g, 2.05 mmol), and DIPEA (1.24 g, 9.63 mmol) were combined in CH₂Cl₂ (10 mL). TiCl₄ (1.90 mmol in CH₂Cl₂) was added dropwise over a 5 min period. The resulting dark solution was stirred for 3 h at which time sodium cyanoborohydride (6.35 mmol) in methanol (5 mL) was added in one portion, and the brown solution stirred for an additional 45 min. The reaction mixture was diluted with ethyl acetate, poured onto a bed of MgSO₄ and filtered. Concentration and purification by flash chromatography (50% ethyl acetate/hexanes) afforded 4-(pyridin-2-ylsulfanyl)-2(*S*)-[2,2,2-

trifluoro-1-(4-fluorophenyl)ethylamino]butyric acid methyl ester as a mixture of diastereomers.

Step 6

[0287] 4-(Pyridin-2-ylsulfanyl)-2(*S*)-[2,2,2-trifluoro-1-(4-fluorophenyl)ethylamino]butyric acid methyl ester was dissolved in methanol (2 mL) and 1N NaOH (1.2 mL) was added. After stirring for 2 h, methanol was removed and the aqueous layer was acidified to pH 5. After extracting with ethyl acetate the organic layer was dried and concentrated to give 4-(pyridin-2-ylsulfanyl)-2(*S*)-[2,2,2-trifluoro-1-(4-fluorophenyl)ethylamino]butyric acid as an oil which was then converted to the title compound as described above. MS (485.5 M+1)

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Biological Examples

Example 1

Cathepsin B Assay

[0288] Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 min. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

[0289] Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity.

Example 2

Cathepsin K Assay

[0290] Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in

25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 min. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

[0291] Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin K inhibitory activity.

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Example 3

Cathepsin L Assay

[0292] Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 min. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

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[0293] Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin L inhibitory activity.

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Example 4

Cathepsin S Assay

[0294] Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); β -mercaptoethanol, 2.5 mM; and BSA, 0.00%. Human cathepsin S (0.05 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Val-Val-Arg-AMC (4 nMoles in 25 μ L of

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assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (at λ 460 nm) for 5 min. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

[0295] Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin S inhibitory activity of $< \text{or} = 100 \text{ nm}$.

Example 5

Cathepsin F Assay

[0296] Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL , comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); DTT, 2.5 mM; and BSA, 0.01%. Human cathepsin F (0.1 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Phe-Arg-AMC (2 nmoles in 25 μL of assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (at λ 460 nm) for 5 min. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

[0297] Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin F inhibitory activity.

Formulation Examples

Example 1

Representative pharmaceutical formulations Containing a Compound of Formula (I)

ORAL FORMULATION

25	Compound of Formula (I)	10-100 mg
	Citric Acid Monohydrate	105 mg
	Sodium Hydroxide	18 mg
	Flavoring	
	Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

30	Compound of Formula (I)	0.1-10 mg
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Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

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TABLET FORMULATION

Compound of Formula (I)	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%

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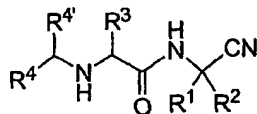
[0298] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

20

WE CLAIM:

1 1. A compound of Formula (I):

2



3

4

(I)

5 R¹ is hydrogen, alkyl, or haloalkyl;

6 R² is hydrogen, alkyl, or haloalkyl; or

7 R¹ and R² taken together with the carbon atom to which R¹ and R² are attached form
8 cycloalkylene optionally substituted with one to four fluoro, piperidin-4-yl wherein the
9 nitrogen atom of the piperidinyl ring is substituted with alkyl, haloalkyl, or cycloalkyl,
10 tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1,1-dioxohexahydrothiopyran-4-yl, or -CH₂-
11 O-CH₂-;

12 R³ is -alkylene-SO₂-alkyl, -alkylene-SO₂-haloalkyl, , -alkylene-SO₂-cycloalkyl, -
13 alkylene-SO₂-cycloalkylalkyl, -alkylene-SO₂-aryl, -alkylene-SO₂-aralkyl, -alkylene-SO₂-
14 heterocycloalkyl, -alkylene-SO₂-heterocycloalkylalkyl, -alkylene-SO₂-heteroaryl, -alkylene-
15 SO₂-heteroaralkyl, -alkylene-SO₂-haloalkylene-aryl or -alkylene-SO₂-haloalkylene-heteroaryl
16 wherein the aromatic or alicyclic ring in R³ is optionally substituted with one, two, or three
17 R^a independently selected from alkyl, alkylsulfonyl, haloalkyl, alkoxy, hydroxy,
18 hydroxyalkyl, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl,
19 cycloalkyl, amino, alkylamino, dialkylamino, aminocarbonyl, or acyl and further wherein the
20 aromatic ring in R^a is optionally substituted with one, two, or three R^b independently selected
21 from alkyl, alkoxy, alkylsulfonyl, hydroxy, or halo;

22 R⁴ is hydrogen, alkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl attached via a
23 carbon ring atom wherein the aromatic or alicyclic ring in R⁴ is optionally substituted by one,
24 two, or three R^f independently selected from alkyl, halo, hydroxy, alkoxy, alkylcarbonyl,
25 alkylsulfonyl, alkylsulfonylamino, aminocarbonyl, haloalkyl, haloalkoxy, carboxy, or
26 alkoxycarbonyl;

27 R^{4'} is difluoromethyl, trifluoromethyl, 1,1,2,2,2-pentafluoroethyl,
28 chlorodifluoromethyl, 1,1-dichloro-2,2,2-trifluoroethyl, 1,1,2,2-tetrafluoroethyl,
29 trichloromethyl, dichlorofluoromethyl, 1,1,2,2,3,3,3-heptafluoropropyl, or 1,1,2,2,3,3-
30 hexafluoropropyl, or a pharmaceutically acceptable salt thereof provided that:

- 31 (a) when R^1 and R^2 taken together with the carbon atom to which R^1 and R^2 are
32 attached form cyclopropylene, R^3 is phenylmethanesulfonylmethyl,
33 cyclopropylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, 2-
34 difluoromethoxyphenylmethanesulfonylmethyl, or 2-trifluoromethylpyridin-6-
35 methanesulfonylmethyl, R^4 is phenyl, 4-hydroxyphenyl, 3-bromophenyl, 4-fluorophenyl, 3-
36 chloro-4-hydroxyphenyl, 3,4-difluorophenyl, or 3,4,5-trifluorophenyl, then $R^{4'}$ is not
37 trifluoromethyl or difluoromethyl;
- 38 (b) when R^1 and R^2 taken together with the carbon atom to which R^1 and R^2 are
39 attached form cyclopropylene, R^3 is phenylmethanesulfonylmethyl,
40 difluoromethoxyphenylmethanesulfonylmethyl, or cyclopropylmethanesulfonylmethyl, R^4 is
41 furan-2-yl, indol-3-yl, thiophen-2-yl, 1-methylpyrrol-2-yl, pyridin-2-yl, thiophen-3-yl or 1-
42 oxo-1-methylpyrrol-2-yl, then $R^{4'}$ is not difluoromethyl or trifluoromethyl;
- 43 (c) when R^1 and R^2 taken together with the carbon atom to which R^1 and R^2 are
44 attached form 1,1-dioxohexahydrothiopyran-4-yl, R^3 is phenylmethanesulfonylmethyl, 4-
45 fluorophenylmethanesulfonylmethyl, or difluoromethoxyphenylmethanesulfonylmethyl, then
46 $R^{4'}$ is not trifluoromethyl; and
- 47 (d) when R^1 and R^2 taken together with the carbon atom to which R^1 and R^2 are
48 attached form tetrahydropyran-4-yl or tetrahydrothiopyran-4-yl, R^3 is
49 cyclopropylmethanesulfonylmethyl or difluoromethoxyphenylmethanesulfonylmethyl, R^4 is
50 4-fluorophenyl, then $R^{4'}$ is not trifluoromethyl.

1 2. The compound of Claim 1 wherein R^3 is -alkylene-SO₂-haloalkylene-heteroaryl.

1 3. The compound of Claim 1 wherein:

2 R^1 and R^2 are cyclopropylene;

3 R^3 is 4-CF₃-pyridin-3-ylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl,
4 pyridazin-3-ylmethanesulfonylmethyl, 2-CF₃-furan-5-ylmethanesulfonylmethyl, pyrimidin-5-
5 ylmethanesulfonylmethyl, 2-CH₃-thiazol-4-ylmethanesulfonylmethyl, pyridin-4-ylmethane-
6 sulfonylmethyl, pyrimidin-4-ylmethanesulfonylmethyl, 2-(1-oxopyrrol-1-yl)ethanesulfonyl-
7 methyl, cyclopropylmethanesulfonylmethyl, 3,3,3-trifluoropropane-1-sulfonylmethyl, 2-CF₃-
8 pyridin-5-ylmethanesulfonylmethyl, 4-[1.2.4]-triazol-1-ylphenylmethanesulfonylmethyl, 2-
9 (2-oxo-2,3-dihydrobenzimidazol-1-yl)-ethanesulfonylmethyl, 5-oxopyrrolidin-2-ylmethane-
10 sulfonylmethyl, 2-F-pyridin-3-ylmethanesulfonylmethyl, 3-CH₃-oxetan-3-ylmethanesulfonyl-
11 methyl, 2-phenylethanesulfonylmethyl, fluoro-pyridin-2-ylmethanesulfonylmethyl, fluoro-

12 pyrazin-2-ylmethanesulfonylmethyl, difluoro-pyridin-2-ylmethanesulfonylmethyl, difluoro-
13 pyridin-3-ylmethanesulfonylmethyl, quinolin-2-ylmethanesulfonylmethyl,
14 benzo[1.2.5]thiadiazol-4-ylmethanesulfonylmethyl, benzothiazol-2-
15 ylmethanesulfonylmethyl, 5-methylisoxazol-3-ylmethanesulfonylmethyl, 2-methylpropyl-
16 sulfonylmethyl, 2,6-difluorophenylmethanesulfonylmethyl, 2,4-difluorophenylmethane-
17 sulfonylmethyl, quinolin-3-ylmethanesulfonylmethyl, 4,4,4-trifluorobutyl-1-sulfonylmethyl,
18 2-CF₃-phenylmethanesulfonylmethyl, 2-CF₃O-phenylmethanesulfonylmethyl, 2-pyridin-2-
19 ylethanesulfonylmethyl, 2-pyridin-3-ylethanesulfonylmethyl, quinolin-8-ylmethane-
20 sulfonylmethyl, 5-methyl-3-phenylisoxazol-4-ylmethanesulfonylmethyl, 4-methyl-2-phenyl-
21 [1.2.3]triazol-5-ylmethanesulfonylmethyl, 2-cyanophenylmethanesulfonylmethyl, 3-
22 methoxycarbonylphenylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, 1-
23 oxopyridin-2-ylmethanesulfonylmethyl, 1-oxopyridin-3-ylmethanesulfonylmethyl,
24 quinoxalin-2-ylmethanesulfonylmethyl, tetrahydropyran-2*RS*-ylmethanesulfonylmethyl, 2,6-
25 dichloro-phenylmethanesulfonylmethyl, 3-methoxycarbonyl-furan-2-yl-
26 methanesulfonylmethyl, 5-methylisoxazol-3-ylmethanesulfonylmethyl, 2,2-
27 dimethylpropylsulfonylmethyl, ethanesulfonylmethyl, methanesulfonylmethyl, propane-1-
28 sulfonylmethyl, 1*H*-indol-2-ylmethanesulfonylmethyl, 2-(1*H*-indol-3-
29 yl)ethanesulfonylmethyl, 2,2,2-trifluoroethanesulfonylmethyl, benzisoxazol-3-
30 ylmethanesulfonylmethyl, 2-tert-butyl-[1.3.4]thiadiazol-5-ylmethanesulfonylmethyl, 2,4,6-
31 trifluorophenylmethanesulfonylmethyl, 2-pyridin-2-ylethanesulfonylmethyl, 1-ethyl-2,5-
32 dioxopyrrolidin-3-ylmethanesulfonylmethyl or benzisoxazol-3-ylmethanesulfonylmethyl;
33 and
34 R⁴ is 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, or
35 3,5-difluorophenyl.

1 4. The compound of Claim 1 wherein:

2 R^{4'} is difluoromethyl, trifluoromethyl, 1,1,2,2,2-pentafluoroethyl,
3 chlorodifluoromethyl, 1,1-dichloro-2,2,2-trifluoroethyl, 1,1,2,2-tetrafluoroethyl,
4 trichloromethyl, dichlorofluoromethyl, 1,1,2,2,3,3,3-heptafluoropropyl, or 1,1,2,2,3,3-
5 hexafluoropropyl; and
6 R⁴ is hydrogen.

1 5. The compound of Claim 1 wherein:

2 $R^{4'}$ is difluoromethyl, trifluoromethyl, 1,1,2,2,2-pentafluoroethyl,
 3 chlorodifluoromethyl, 1,1-dichloro-2,2,2-trifluoroethyl, 1,1,2,2-tetrafluoroethyl,
 4 trichloromethyl, dichlorofluoromethyl, 1,1,2,2,3,3,3-heptafluoropropyl, or 1,1,2,2,3,3-
 5 hexafluoropropyl; and
 6 R^4 is alkyl.

1 6. The compound of Claim 1 wherein:

2 $R^{4'}$ is difluoromethyl, trifluoromethyl, 1,1,2,2,2-pentafluoroethyl,
 3 chlorodifluoromethyl, 1,1-dichloro-2,2,2-trifluoroethyl, 1,1,2,2-tetrafluoroethyl,
 4 trichloromethyl, dichlorofluoromethyl, 1,1,2,2,3,3,3-heptafluoropropyl, or 1,1,2,2,3,3-
 5 hexafluoropropyl; and
 6 R^4 is haloalkyl.

1 7. The compound of Claim 1, 4, 5, or 6 wherein R^3 is 3,5-dimethylisoxazol-4-
 2 ylmethanesulfonylmethyl; 2-CF₃methylphenylmethane-sulfonylmethyl, 3-CF₃pyridin-2-
 3 ylmethanesulfonylmethyl, 2-F-furan-5-ylmethanesulfonyl-methyl, 2-methylthiazol-4-
 4 ylmethanesulfonylmethyl, tetrahydropyran-4-ylmethane-sulfonylmethyl, 1,1-dioxo-1λ⁶-
 5 hexahydrothiopyran-4-ylmethanesulfonylmethyl, 1-ethylpiperidin-4-
 6 ylmethanesulfonylmethyl, 2-oxo-tetrahydropyrimidin-4-ylmethane-sulfonylmethyl, 1-ethyl-
 7 2-oxopiperidin-4-ylmethanesulfonylmethyl, 1-acetyl piperidin-4-ylmethanesulfonylmethyl, 1-
 8 ethoxycarbonylpiperidin-4-ylmethanesulfonylmethyl, 1-methylsulfonylpiperidin-4-
 9 ylmethanesulfonylmethyl, 1-cyclopropylpiperidin-4-ylmethane-sulfonylmethyl, 1-
 10 acetylazetidin-3-ylmethanesulfonylmethyl, 1-ethoxycarbonylazetidin-3-
 11 ylmethanesulfonylmethyl, 1-methylsulfonylazetidin-3-ylmethanesulfonylmethyl, 1-
 12 ethylazetidin-3-ylmethanesulfonylmethyl, 1-cyclopropylazetidin-3-ylmethanesulfonylmethyl
 13 furan-2-ylmethanesulfonylmethyl, difluoro-(4-fluorophenyl)methanesulfonylmethyl,
 14 difluoro-(pyrazin-2-yl)methanesulfonylmethyl, difluoro-(2-difluoromethoxyphenyl)-
 15 methanesulfonylmethyl, 1-acetyl piperidin-4-ylsulfonylmethyl, 1-ethoxycarbonylpiperidin-4-
 16 ylsulfonylmethyl, 1-cyclopropylpiperidin-4-ylsulfonylmethyl, 2-(pyridin-2-
 17 yl)ethanesulfonyl-methyl, 2-(pyridin-3-yl)ethanesulfonylmethyl, 2-(pyridin-4-
 18 yl)ethanesulfonylmethyl, 3-(pyridin-2-yl)propanesulfonylmethyl, 2,6-
 19 difluorophenylmethanesulfonyl, [1.3.5]triazin-2-ylmethanesulfonylmethyl, [1.3.4]thiadiazol-
 20 2-ylmethanesulfonylmethyl, oxazol-5-ylmethane-sulfonylmethyl, thiazol-5-
 21 ylmethanesulfonylmethyl, 4-fluorophenylmethanesulfonylmethyl, 4-

22 aminocarbonylphenylmethanesulfonylmethyl, 4-piperazin-4-ylphenylmethanesulfonylmethyl,
23 5-fluoroindol-3-ylmethanesulfonylmethyl, 4,6-difluoroindol-3-ylmethanesulfonylmethyl, 1-
24 methylindol-3-ylmethanesulfonylmethyl, 4-fluoroindol-3-ylmethanesulfonylmethyl, 2-(5-
25 fluoroindol-3-yl)ethanesulfonylmethyl, 2-(4,6-difluoroindol-3-yl)ethanesulfonylmethyl, 2-(1-
26 methylindol-3-yl)ethanesulfonylmethyl, 2-(4-fluoroindol-3-yl)ethanesulfonylmethyl, 2-
27 quinolin-3-ylethanesulfonylmethyl, 2-quinolin-2-ylethanesulfonylmethyl, isoquinolin-3-
28 ylmethane-sulfonylmethyl, 2-(isoquinolin-3-yl)ethanesulfonylmethyl, 2,4-difluoropyridin-3-
29 ylmethane-sulfonylmethyl, 3,4-difluoropyridin-4-ylmethanesulfonylmethyl, 2-(2,4-
30 difluoropyridin-3-yl)ethanesulfonylmethyl, 2-(3,4-difluoropyridin-4-yl)ethanesulfonylmethyl,
31 fluoro-(2,4-difluoropyridin-3-yl)methanesulfonylmethyl, fluoro-(3,4-difluoropyridin-4-
32 yl)methane-sulfonylmethyl, 2,4-diCF₃pyridin-3-ylmethanesulfonylmethyl, 3,4-diCF₃pyridin-
33 4-ylmethane-sulfonylmethyl, 2-(2,4-diCF₃pyridin-3-yl)ethanesulfonylmethyl, 2-(3,4-
34 diCF₃pyridin-4-yl)ethanesulfonylmethyl, fluoro-(2,4-diCF₃pyridin-3-
35 yl)methanesulfonylmethyl, fluoro-(3,4-diCF₃pyridin-4-yl)methanesulfonylmethyl, 4-F-
36 pyridin-3-ylmethanesulfonylmethyl, 3-F-pyridin-5-ylmethanesulfonylmethyl, 2-F-pyridin-5-
37 ylmethanesulfonylmethyl, 2-F-pyridin-3-ylmethanesulfonylmethyl, 5-F-pyridin-2-
38 ylmethanesulfonylmethyl, 4-F-pyridin-2-ylmethane-sulfonylmethyl, 4-F-1-oxopyridin-3-
39 ylmethanesulfonylmethyl, 3-F-1-oxopyridin-5-ylmethane-sulfonylmethyl, 2-F-1-oxopyridin-
40 5-ylmethanesulfonylmethyl, 2-F-1-oxopyridin-3-ylmethane-sulfonylmethyl, 5-F-1-
41 oxopyridin-2-ylmethanesulfonylmethyl, 4-F-1-oxopyridin-2-ylmethane-sulfonylmethyl, 4-
42 CF₃-pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-pyridin-5-ylmethane-sulfonylmethyl, 3-F-
43 pyridin-2-ylmethanesulfonylmethyl, 2-CF₃-pyridin-3-ylmethane-sulfonylmethyl, 4-CF₃-1-
44 oxopyridin-2-ylmethanesulfonylmethyl, 3-CF₃-1-oxopyridin-5-ylmethanesulfonylmethyl, 3-
45 F-1-oxopyridin-2-ylmethanesulfonylmethyl, 2-CF₃-1-oxopyridin-3-ylmethanesulfonylmethyl,
46 5-CF₃-1-oxopyridin-2-ylmethanesulfonylmethyl, 2-CH₃-pyridin-6-ylmethanesulfonylmethyl,
47 3-CH₃-pyridin-2-ylmethanesulfonylmethyl, 4-CH₃-pyridin-3-ylmethanesulfonylmethyl, 3-
48 CH₃-pyridin-4-ylmethanesulfonylmethyl, 2-(2-CH₃-pyridin-6-yl)ethanesulfonylmethyl, 2-(3-
49 CF₃-pyridin-2-yl)ethanesulfonylmethyl, 2-(4-CF₃-pyridin-3-yl)ethanesulfonylmethyl, 2-(3-
50 CF₃-pyridin-4-yl)ethanesulfonylmethyl, 2-C₂H₅-pyridin-6-ylmethanesulfonylmethyl, 3-C₂H₅-
51 pyridin-2-ylmethanesulfonylmethyl, 4-C₂H₅-pyridin-3-ylmethanesulfonylmethyl, 3-C₂H₅-
52 pyridin-4-ylmethanesulfonylmethyl, 2-(2-C₂H₅-pyridin-6-yl)ethanesulfonylmethyl, 2-(3-
53 C₂H₅-pyridin-2-yl)ethanesulfonylmethyl, 2-(4-C₂H₅-pyridin-3-yl)ethanesulfonylmethyl, 2-(3-
54 C₂H₅-pyridin-4-yl)ethanesulfonylmethyl, 2-(2-CH₃-pyridin-3-yl)ethanesulfonylmethyl, 2-
55 CF₃-pyridin-3-ylmethanesulfonylmethyl, 2-(3-CF₃-pyridin-4-yl)ethanesulfonylmethyl, 3-CF₃-

pyridin-4-ylmethanesulfonylmethyl, cinnolin-3-ylmethane-sulfonylmethyl, 2-(cinnolin-3-yl)ethanesulfonylmethyl, phthalazin-1-ylmethanesulfonylmethyl, 2-(phthalazin-1-yl)ethanesulfonylmethyl, 2-(quinoxalin-2-yl)ethanesulfonylmethyl, quinazolin-2-ylmethanesulfonylmethyl, 2-(quinazolin-2-yl)ethanesulfonylmethyl, [1,8]naphthyridin-2-ylmethanesulfonylmethyl, 2-([1,8]naphthyridin-2-yl)ethanesulfonylmethyl, [1,8]naphthyridin-3-ylmethanesulfonylmethyl, 2-([1,8]naphthyridin-3-yl)ethanesulfonylmethyl, 3-Cl-pyridin-2-ylmethanesulfonylmethyl, 4-Cl-pyridin-3-ylmethanesulfonylmethyl, 3-Cl-pyridin-4-ylmethane-sulfonylmethyl, 3-F-pyridin-2-ylmethanesulfonylmethyl, 4-F-pyridin-3-ylmethanesulfonyl-methyl, 3-F-pyridin-4-ylmethanesulfonylmethyl, isoquinolin-4-ylmethanesulfonylmethyl, 6-phenylpyridin-2-ylmethanesulfonylmethyl, 3-phenylpyridin-2-ylmethanesulfonylmethyl, 4-phenylpyridin-3-ylmethanesulfonylmethyl, 3-phenylpyridin-4-ylmethanesulfonylmethyl, 2-(6-phenylpyridin-2-yl)ethanesulfonylmethyl, 2-(3-phenylpyridin-2-yl)ethanesulfonylmethyl, 2-(4-phenylpyridin-3-yl)ethanesulfonylmethyl, 2-(3-phenylpyridin-4-yl)ethanesulfonylmethyl, 6-(pyridin-2-yl)pyridin-2-ylmethanesulfonylmethyl, 3-(pyridin-2-yl)pyridin-2-ylmethane-sulfonylmethyl, 4-(pyridin-2-yl)pyridin-3-ylmethanesulfonylmethyl, 3-(pyridin-2-yl)pyridin-4-ylmethanesulfonylmethyl, 2-[6-(pyridin-2-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[3-(pyridin-2-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[4-(pyridin-2-yl)pyridin-3-yl]ethanesulfonylmethyl, 2-[3-(pyridin-2-yl)pyridin-4-yl]ethanesulfonylmethyl, 6-(pyridin-3-yl)pyridin-2-ylmethane-sulfonylmethyl, 3-(pyridin-3-yl)pyridin-2-ylmethanesulfonylmethyl, 4-(pyridin-3-yl)pyridin-3-ylmethanesulfonylmethyl, 3-(pyridin-3-yl)pyridin-4-ylmethanesulfonylmethyl, 2-[6-(pyridin-3-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[3-(pyridin-3-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[4-(pyridin-3-yl)pyridin-3-yl]ethanesulfonylmethyl, 2-[3-(pyridin-3-yl)pyridin-4-yl]ethanesulfonylmethyl, 6-(pyridin-4-yl)pyridin-2-ylmethanesulfonylmethyl, 3-(pyridin-4-yl)pyridin-2-ylmethanesulfonylmethyl, 4-(pyridin-4-yl)pyridin-3-ylmethanesulfonylmethyl, 3-(pyridin-4-yl)pyridin-4-ylmethanesulfonylmethyl, 2-[6-(pyridin-4-yl)pyridin-2-yl]-ethanesulfonylmethyl, 2-[3-(pyridin-4-yl)pyridin-2-yl]ethanesulfonylmethyl, 2-[4-(pyridin-4-yl)pyridin-3-yl]ethanesulfonylmethyl, 2-[3-(pyridin-4-yl)pyridin-4-yl]ethanesulfonylmethyl, 2,2-dimethylcyclopropylmethanesulfonylmethyl, biphen-2-ylmethanesulfonylmethyl, 2-thiophen-2-ylphenylmethanesulfonylmethyl, 2-thiazol-2-ylphenylmethanesulfonylmethyl, 2-thiazol-5-ylphenylmethanesulfonylmethyl, 2-[1.2.3]thiadiazol-5-ylphenylmethane-sulfonylmethyl, 2-isoxazol-5-ylphenylmethanesulfonylmethyl, 2-(1-methylpyrazol-5-yl)phenylmethanesulfonylmethyl, 2-[1.2.3]triazol-5-ylphenylmethanesulfonylmethyl, 2-

90 [1.2.3]oxadiazol-5-ylphenylmethanesulfonylmethyl, 2-[(1.2.3)triazol-5-
91 yl]phenylmethanesulfonylmethyl, 2-[(1.2.3)triazol-1-yl]phenylmethanesulfonylmethyl,
92 oxazolo[5,4-b]pyridin-2-ylmethane-sulfonylmethyl, oxazolo[4,5-c]pyridin-2-
93 ylmethanesulfonylmethyl, oxazolo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, benzimidazol-
94 5-ylmethanesulfonylmethyl, benzimidazol-4-ylmethanesulfonylmethyl, 3*H*-imidazo[4,5-
95 b]pyridin-2-ylmethanesulfonylmethyl, 3*H*-imidazo[4,5-c]pyridin-2-ylmethanesulfonylmethyl,
96 3-CF₃-3*H*-imidazo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-3*H*-imidazo[4,5-
97 c]pyridin-2-ylmethanesulfonylmethyl, 1-CF₃-1*H*-imidazo[4,5-c]pyridin-2-
98 ylmethanesulfonylmethyl, 1-CF₃-1*H*-imidazo[4,5-b]pyridin-2-ylmethanesulfonylmethyl,
99 thiazolo[5,4-b]pyridin-2-ylmethanesulfonylmethyl, thiazolo[4,5-c]pyridin-2-
100 ylmethanesulfonylmethyl, thiazolo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, 5-
101 CF₃thiazolo[5,4-b]pyridin-2-ylmethanesulfonylmethyl, 4-CF₃-thiazolo[4,5-c]pyridin-2-
102 ylmethanesulfonylmethyl, 7-CF₃-thiazolo[4,5-b]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-
103 1*H*-pyrrolo[2,3-b]pyridin-2-ylmethanesulfonylmethyl, 3-CF₃-1*H*-pyrrolo[3,2-c]pyridin-2-
104 ylmethanesulfonylmethyl, 3-CF₃-1*H*-pyrrolo[3,2-b]pyridin-2-ylmethanesulfonylmethyl,
105 imidazo[1,2-c]pyrimidin-2-methanesulfonylmethyl, 8-CF₃-imidazo[1,2-c]pyrimidin-2-
106 methanesulfonylmethyl, imidazo[1,2-a]pyrimidin-2-methanesulfonylmethyl, 8-CF₃-
107 imidazo[1,2-b]pyridazin-2-ylmethanesulfonylmethyl, imidazo[1,2-a]pyrazin-2-
108 methanesulfonylmethyl, 8-CF₃-imidazo[1,2-a]pyrazin-2-methanesulfonylmethyl,
109 pyrazolo[1,5-c]pyrimidin-2-ylmethanesulfonylmethyl, 3-CF₃-pyrazolo[1,5-c]pyrimidin-2-
110 ylmethanesulfonylmethyl, 4-CF₃-pyrazolo[1,5-c]pyrimidin-2-ylmethanesulfonylmethyl,
111 imidazo[1,2-d][1,2,4]triazin-2-methanesulfonylmethyl, 3-CF₃-imidazo[1,2-d][1,2,4]triazin-2-
112 methanesulfonylmethyl, [1,3]benzoxazol-2-ylmethanesulfonylmethyl, 5-F-[1,3]benzoxazol-
113 2-ylmethanesulfonylmethyl [1,3]benzoxazol-4-ylmethanesulfonylmethyl, 2-CF₃-
114 [1,3]benzoxazol-4-ylmethanesulfonyl-methyl, [1,3]benzoxazol-7-ylmethanesulfonylmethyl,
115 2-CF₃-[1,3]benzoxazol-7-ylmethane-sulfonylmethyl, [1,2]benzoxazol-3-
116 ylmethanesulfonylmethyl, [1,2]benzoxazol-4-ylmethanesulfonylmethyl, 5-CF₃-
117 [1,2]benzoxazol-4-ylmethanesulfonylmethyl, 3-CF₃-[1,2]benzoxazol-4-
118 ylmethanesulfonylmethyl, 6-CF₃-[1,2]benzoxazol-7-ylmethane-sulfonylmethyl, 6-CN-
119 [1,2]benzoxazol-7-ylmethanesulfonylmethyl, 3-CF₃-[1,2]benzoxazol-7-
120 ylmethanesulfonylmethyl, 5-F-[1,2]benzoxazol-3-ylmethanesulfonylmethyl, [2,3]benzoxazol-
121 7-ylmethanesulfonylmethyl, 6-CF₃-[2,3]benzoxazol-7-ylmethanesulfonylmethyl, 1-CF₃-
122 [2,3]benzoxazol-7-ylmethanesulfonylmethyl, 5-CF₃-[2,3]benzoxazol-4-ylmethane-
123 sulfonylmethyl, 5-CN-[2,3]benzoxazol-4-ylmethanesulfonylmethyl, 1-CF₃-[2,3]benzoxazol-

124 4-ylmethanesulfonylmethyl, benzothiazol-2-ylmethanesulfonylmethyl, 5-F-benzothiazol-2-
125 ylmethanesulfonylmethyl, benzothiazol-4-ylmethanesulfonylmethyl, 2-CF₃-benzothiazol-4-
126 ylmethanesulfonylmethyl, benzothiazol-7-ylmethanesulfonylmethyl, 2-CF₃-benzothiazol-7-
127 ylmethanesulfonylmethyl, [1,2]benzothiazol-3-ylmethanesulfonylmethyl, [1,2]benzothiazol-
128 4-ylmethanesulfonylmethyl, 5-CF₃-[1,2]benzothiazol-4-ylmethanesulfonylmethyl, 3-CF₃-
129 [1,2]benzothiazol-4-ylmethanesulfonylmethyl, 6-CF₃-[1,2]benzothiazol-7-ylmethane-
130 sulfonylmethyl, 6-CN-[1,2]benzothiazol-7-ylmethanesulfonylmethyl, 3-CF₃-
131 [1,2]benzothiazol-7-ylmethanesulfonylmethyl, 5-F-[1,2]benzothiazol-3-
132 ylmethanesulfonylmethyl, [2,3]benzothiazol-7-ylmethanesulfonylmethyl, 6-CF₃-
133 [2,3]benzothiazol-7-ylmethane-sulfonylmethyl, 1-CF₃-[2,3]benzothiazol-7-
134 ylmethanesulfonylmethyl, 5-CF₃-[2,3]benzothiazol-4-ylmethanesulfonylmethyl, 5-CN-
135 [2,3]benzothiazol-4-ylmethanesulfonylmethyl, 1-CF₃-[2,3]benzothiazol-4-
136 ylmethanesulfonylmethyl, 4-CF₃-2-CH₃-thiazol-5-ylmethanesulfonylmethyl, 4-CF₃-thiazol-5-
137 ylmethanesulfonylmethyl, 4-CF₃-2-phenyl-thiazol-5-ylmethanesulfonylmethyl, 5-CF₃-2-CH₃-
138 thiazol-4-ylmethanesulfonylmethyl, 5-CF₃-thiazol-4-ylmethanesulfonylmethyl, 5-CF₃-2-
139 phenyl-thiazol-4-ylmethanesulfonylmethyl, 5-CH₃-thiazol-2-ylmethanesulfonylmethyl, 5-
140 CF₃-thiazol-2-ylmethanesulfonylmethyl, 5-phenyl-thiazol-2-ylmethanesulfonylmethyl, 4-
141 CH₃-thiazol-2-ylmethanesulfonylmethyl, 4-CF₃-thiazol-2-ylmethanesulfonylmethyl, 4-
142 phenyl-thiazol-2-ylmethanesulfonylmethyl, 5-CH₃-2-(pyridin-2-yl)-[1,2,3]triazol-4-
143 ylmethanesulfonylmethyl, 5-CF₃-2-(pyridin-2-yl)-[1,2,3]triazol-4-ylmethanesulfonylmethyl,
144 5-CF₃-2-(4-methylsulfonylphenyl)-[1,2,3]triazol-4-ylmethane-sulfonylmethyl, 4,5-dimethyl-
145 [1,2,4]triazol-3-ylmethanesulfonylmethyl, 5-CF₃-4-CH₃-[1,2,4]triazol-3-
146 ylmethanesulfonylmethyl, 4-CH₃-5-phenyl-[1,2,4]triazol-3-ylmethane-sulfonylmethyl, 5-
147 CF₃-4-cyclopropyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 2,5-dimethyl-[1,2,4]triazol-3-
148 ylmethanesulfonylmethyl, 5-CF₃-2-CH₃-[1,2,4]triazol-3-ylmethane-sulfonylmethyl, 2-CH₃-5-
149 phenyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 2-cyclopropyl-5-phenyl-[1,2,4]triazol-3-
150 ylmethanesulfonylmethyl, 5-CF₃-1-CH₃-[1,2,4]triazol-3-ylmethane-sulfonylmethyl, 1-CH₃-5-
151 phenyl-[1,2,4]triazol-3-ylmethanesulfonylmethyl, 5-CH₃-1-phenyl-[1,2,4]triazol-3-
152 ylmethanesulfonylmethyl, 3-CH₃-[1,2,4]oxadiazol-5-ylmethanesulfonylmethyl 3-CF₃-
153 [1,2,4]oxadiazol-5-ylmethanesulfonylmethyl, 3-phenyl-[1,2,4]oxadiazol-5-ylmethane-
154 sulfonylmethyl, 5-CH₃-[1,2,4]oxadiazol-3-ylmethanesulfonylmethyl, 5-CF₃-[1,2,4]oxadiazol-
155 3-ylmethanesulfonylmethyl, 5-phenyl-[1,2,4]oxadiazol-3-ylmethanesulfonylmethyl, 2-CH₃-
156 [1,3,4]oxadiazol-5-ylmethanesulfonylmethyl, 2-CF₃-[1,3,4]oxadiazol-5-ylmethane-
157 sulfonylmethyl, 2-phenyl-[1,3,4]oxadiazol-5-ylmethanesulfonylmethyl, 3-CH₃-

158 [1,2,4]thiadiazol-5-ylmethanesulfonylmethyl, 3-CF₃-[1,2,4]thiadiazol-5-
159 ylmethanesulfonylmethyl, 3-phenyl-[1,2,4]thiadiazol-5-ylmethanesulfonylmethyl, 5-CH₃-
160 [1,2,4]thiadiazol-3-ylmethane-sulfonylmethyl, 5-CF₃-[1,2,4]thiadiazol-3-
161 ylmethanesulfonylmethyl, 5-phenyl-[1,2,4]thiadiazol-3-ylmethanesulfonylmethyl, 2-CH₃-
162 [1,3,4]thiadiazol-5-ylmethanesulfonylmethyl, 2-CF₃-[1,3,4]thiadiazol-5-
163 ylmethanesulfonylmethyl, 2-phenyl-[1,3,4]thiadiazol-5-ylmethane-sulfonylmethyl, 2,2-
164 difluoropyrrolidinylmethanesulfonylmethyl, 3,3-difluoropyrrolidinyl-methanesulfonylmethyl,
165 3-CF₃-*N*-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 3-CN-*N*-CH₃-pyrrol-2-
166 ylmethanesulfonylmethyl, 4-CF₃-*N*-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 4-(1-CH₃-1-
167 hydroxyethyl)-*N*-CH₃-pyrrol-2-ylmethanesulfonylmethyl, 1,3-dimethylpyrrol-2-ylmethane-
168 sulfonylmethyl, 4-CF₃-*N*-CH₃-pyrrol-3-ylmethanesulfonylmethyl, 4-CN-*N*-CH₃-pyrrol-3-
169 ylmethanesulfonylmethyl, 4-CN-*N*-(3,3,3-trifluoropropyl)-pyrrol-3-
170 ylmethanesulfonylmethyl, 2-CF₃-*N*-CH₃-pyrrol-3-ylmethanesulfonylmethyl, 2-CF₃-*N*-phenyl-
171 pyrrol-3-ylmethane-sulfonylmethyl, 4-CF₃-pyrrol-2-ylmethanesulfonylmethyl, 4-(1-CH₃-1-
172 hydroxyethyl)-pyrrol-2-ylmethanesulfonylmethyl, 3-CH₃-pyrrol-2-ylmethanesulfonylmethyl,
173 4-CF₃-pyrrol-3-ylmethane-sulfonylmethyl, 2-CF₃-pyrrol-3-ylmethanesulfonylmethyl, 3-CF₃-
174 pyrrol-2-ylmethane-sulfonylmethyl, 2-CF₃-pyrrol-4-ylmethanesulfonylmethyl, 2-CF₃-*N*-CH₃-
175 pyrrol-4-ylmethane-sulfonylmethyl, 3-CF₃-fur-2-ylmethanesulfonylmethyl, 3-CN-fur-2-
176 ylmethanesulfonylmethyl, 3-CF₃-fur-4-ylmethanesulfonylmethyl, 3-CN-fur-4-
177 ylmethanesulfonylmethyl, 2-CF₃-fur-3-ylmethanesulfonylmethyl, 3-CF₃-thiazol-2-
178 ylmethanesulfonylmethyl, 3-CN-thiazol-2-ylmethanesulfonylmethyl, 3-CF₃-thiazol-4-
179 ylmethanesulfonylmethyl, 3-CN-thiazol-4-ylmethanesulfonylmethyl, 2-CF₃-thiazol-3-
180 ylmethanesulfonylmethyl, *N*-CH₃-3-CF₃-1*H*-pyrazol-5-ylmethanesulfonylmethyl, *N*-CH₃-3-
181 (1-CH₃-1-hydroxyethyl)-1*H*-pyrazol-5-ylmethane-sulfonylmethyl, *N*-CH₃-3-phenyl-1*H*-
182 pyrazol-5-ylmethanesulfonylmethyl, *N*-CH₃-3-CF₃-1*H*-pyrazol-4-ylmethanesulfonylmethyl,
183 *N*-CH₃-4-CN-1*H*-pyrazol-3-ylmethanesulfonylmethyl, *N*-phenyl-4-CN-1*H*-pyrazol-3-
184 ylmethanesulfonylmethyl, *N*-phenyl-3-CF₃-1*H*-pyrazol-4-ylmethanesulfonylmethyl, *N*-
185 phenyl-5-CF₃-1*H*-pyrazol-4-ylmethanesulfonylmethyl, (*N*-CH₃-4-CF₃-1*H*-imidazol-2-
186 ylmethane)-sulfonylmethyl, [*N*-CH₃-4-(1-CH₃-1-hydroxyethyl)-1*H*-imidazol-2-ylmethane]-
187 sulfonylmethyl, (*N*-CH₃-4-phenyl-1*H*-imidazol-2-ylmethane)-sulfonylmethyl, *N*-CH₃-3-CF₃-
188 1*H*-pyrazol-4-ylmethanesulfonylmethyl, (*N*-CH₃-2-CF₃-1*H*-imidazol-5-ylmethane)-
189 sulfonylmethyl, (*N*-CH₃-2-phenyl-1*H*-imidazol-5-ylmethane)-sulfonylmethyl, (*N*-CH₃-5-CF₃-
190 1*H*-imidazol-4-ylmethane)-sulfonylmethyl, (*N*-phenyl-5-CF₃-1*H*-imidazol-4-ylmethane)-
191 sulfonylmethyl, 4-CN-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CN-3-phenyl-[1,2]oxazol-

192 5-ylmethanesulfonylmethyl, 4-CN-[1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CN-5-phenyl-
193 [1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CN-isothiazol-5-ylmethanesulfonylmethyl, 4-CN-
194 3-phenyl-isothiazol-5-ylmethanesulfonylmethyl, 4-CN-isothiazol-3-
195 ylmethanesulfonylmethyl, 4-CN-5-phenyl-isothiazol-3-ylmethane-sulfonylmethyl, 4-CF₃-
196 [1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-3-CH₃-[1,2]oxazol-5-
197 ylmethanesulfonylmethyl, 4-CF₃-3-phenyl-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-
198 [1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CF₃-5-CH₃-[1,2]oxazol-3-
199 ylmethanesulfonylmethyl, 4-CF₃-5-phenyl-[1,2]oxazol-3-ylmethanesulfonylmethyl, 3-CF₃-
200 [1,2]oxazol-4-ylmethanesulfonylmethyl, 5-CF₃-[1,2]oxazol-4-ylmethanesulfonylmethyl, 4-
201 CF₃-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-3-CH₃-[1,2]oxazol-5-
202 ylmethanesulfonylmethyl, 4-CF₃-3-phenyl-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-
203 [1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CF₃-5-CH₃-[1,2]oxazol-3-
204 ylmethanesulfonylmethyl, 4-CF₃-5-phenyl-[1,2]oxazol-3-ylmethanesulfonylmethyl, 3-CF₃-
205 [1,2]oxazol-4-ylmethanesulfonylmethyl, 5-CF₃-[1,2]oxazol-4-ylmethanesulfonylmethyl, 4-
206 CH₃-[1,2]oxazol-5-ylmethanesulfonylmethyl, 4-CH₃-3-phenyl-[1,2]oxazol-5-
207 ylmethanesulfonylmethyl, 4-CH₃-[1,2]oxazol-3-ylmethanesulfonylmethyl, 4-CH₃-5-phenyl-
208 [1,2]oxazol-3-ylmethanesulfonylmethyl, 3-CH₃-[1,2]oxazol-4-ylmethane-sulfonylmethyl, 5-
209 CH₃-[1,2]oxazol-4-ylmethanesulfonylmethyl, 4-CH₃-isothiazol-5-ylmethane-sulfonylmethyl,
210 4-CH₃-3-phenyl-isothiazol-5-ylmethanesulfonylmethyl, 4-CH₃-isothiazol-3-
211 ylmethanesulfonylmethyl, 4-CH₃-5-phenyl-isothiazol-3-ylmethanesulfonylmethyl, 3-CH₃-
212 isothiazol-4-ylmethanesulfonylmethyl, 5-CH₃-isothiazol-4-ylmethanesulfonylmethyl, 4-CF₃-
213 2-CH₃-[1,3]oxazol-5-ylmethanesulfonylmethyl, 4-CF₃-[1,3]oxazol-5-
214 ylmethanesulfonylmethyl, 4-CF₃-2-phenyl-[1,3]oxazol-5-ylmethanesulfonylmethyl, 5-CF₃-2-
215 CH₃-[1,3]oxazol-4-ylmethanesulfonylmethyl, 5-CF₃-[1,3]oxazol-4-
216 ylmethanesulfonylmethyl, 5-CF₃-2-phenyl-[1,3]oxazol-4-ylmethanesulfonylmethyl, 5-CH₃-
217 [1,3]oxazol-2-ylmethanesulfonylmethyl, 5-CF₃-[1,3]oxazol-2-ylmethanesulfonylmethyl, 5-
218 phenyl-[1,3]oxazol-2-ylmethane-sulfonylmethyl, 4-CH₃-[1,3]oxazol-2-
219 ylmethanesulfonylmethyl, 4-CF₃-[1,3]oxazol-2-ylmethanesulfonylmethyl, 4-phenyl-
220 [1,3]oxazol-2-ylmethanesulfonylmethyl, *N*-methyl-indol-2-ylmethanesulfonylmethyl, 3-CF₃-
221 indol-2-ylmethanesulfonylmethyl, 3-CF₃-*N*-methyl-indol-2-ylmethanesulfonylmethyl, 5-
222 fluoro-*N*-methyl-indol-2-ylmethanesulfonylmethyl, *N*-methyl-indol-3-
223 ylmethanesulfonylmethyl, 2-CF₃-indol-3-ylmethanesulfonylmethyl, 2-CF₃-*N*-methyl-indol-3-
224 ylmethanesulfonylmethyl, 5-fluoro-*N*-methyl-indol-3-ylmethanesulfonylmethyl, 5-CF₃-*N*-
225 methyl-indol-4-ylmethanesulfonylmethyl, 5-CN-*N*-methyl-indol-4-ylmethane-

226 sulfonylmethyl, 2-CF₃-*N*-methyl-indol-4-ylmethanesulfonylmethyl, 3-CF₃-*N*-methyl-indol-4-
227 ylmethanesulfonylmethyl, 6-CF₃-*N*-methyl-indol-7-ylmethanesulfonylmethyl, 6-CN-*N*-
228 methyl-indol-7-ylmethanesulfonylmethyl, 2-CF₃-*N*-methyl-indol-7-ylmethanesulfonylmethyl,
229 3-CF₃-*N*-methyl-indol-7-ylmethanesulfonylmethyl, benzofuran-2-ylmethanesulfonylmethyl,
230 3-CF₃-benzofuran-2-ylmethanesulfonylmethyl, 3-CN-benzofuran-2-
231 ylmethanesulfonylmethyl, 5-F-benzofuran-2-ylmethanesulfonylmethyl, benzofuran-3-
232 ylmethanesulfonylmethyl, 2-CF₃-benzofuran-3-ylmethanesulfonylmethyl, 2-CH₃-benzofuran-
233 3-ylmethanesulfonylmethyl, 5-F-benzofuran-3-ylmethanesulfonylmethyl, 5-CF₃-benzofuran-
234 4-ylmethanesulfonylmethyl, 5-CN-benzofuran-4-ylmethanesulfonylmethyl, 2-CF₃-
235 benzofuran-4-ylmethanesulfonylmethyl, 3-CF₃-benzofuran-4-ylmethanesulfonylmethyl, 6-
236 CF₃-benzofuran-7-ylmethanesulfonylmethyl, 6-CN-benzofuran-7-ylmethanesulfonylmethyl,
237 2-CF₃-benzofuran-7-ylmethanesulfonylmethyl, 3-CF₃-benzofuran-7-
238 ylmethanesulfonylmethyl, benzothien-2-ylmethanesulfonylmethyl, (3-CF₃-benzothien-2-
239 ylmethane)-sulfonylmethyl, (3-CN-benzothien-2-ylmethane)-sulfonylmethyl, (5-F-
240 benzothien-2-ylmethane)-sulfonylmethyl, benzothien-3-ylmethanesulfonylmethyl, (2-CF₃-
241 benzothien-3-ylmethane)-sulfonylmethyl, (2-CH₃-benzothien-3-ylmethane)-sulfonylmethyl,
242 (5-fluoro-benzothien-3-ylmethane)-sulfonylmethyl, (5-CF₃-benzothien-4-ylmethane)-
243 sulfonylmethyl, (5-CN-benzothien-4-ylmethane)-sulfonylmethyl, (2-CF₃-benzothien-4-
244 ylmethane)-sulfonylmethyl, (3-CF₃-benzothien-4-ylmethane)-sulfonylmethyl, (6-CF₃-
245 benzothien-7-ylmethane)-sulfonylmethyl, (6-CN-benzothien-7-ylmethane)-sulfonylmethyl,
246 (2-CF₃-benzothien-7-ylmethane)-sulfonylmethyl, (3-CF₃-benzothien-7-ylmethane)-
247 sulfonylmethyl, *N*-methyl-benzimidazol-2-ylmethanesulfonylmethyl, (5-fluoro-*N*-methyl-
248 benzimidazol-2-ylmethane)-sulfonylmethyl, (*N*-methyl-indazol-3-ylmethane)-
249 sulfonylmethyl, (5-fluoro-*N*-methyl-indazol-3-ylmethane)-sulfonylmethyl, (2-CF₃-*N*-methyl-
250 benzimidazol-4-ylmethane)-sulfonylmethyl, (2-CF₃-*N*-methyl-benzimidazol-7-ylmethane)-
251 sulfonylmethyl, (*N*-methyl-indazol-4-ylmethane)-sulfonylmethyl, (5-CF₃-*N*-methyl-indazol-
252 4-ylmethane)-sulfonylmethyl, (3-CF₃-*N*-methyl-indazol-4-ylmethane)-sulfonylmethyl, (6-
253 CF₃-*N*-methyl-indazol-7-ylmethane)-sulfonylmethyl, (6-CN-*N*-methyl-indazol-7-ylmethane)-
254 sulfonylmethyl, or (3-CF₃-*N*-methyl-indazol-7-ylmethane)-sulfonylmethyl.

- 1 8. The compound of Claim 7 wherein R¹ and R² together with the carbon atom to which
2 they are attached form cycloalkylene.

1 9. The compound of Claim 7 wherein R¹ and R² together with the carbon atom to which
2 they are attached form piperidin-4-yl substituted at the nitrogen with ethyl, trifluoroethyl or
3 cyclopropyl.

1 10. The compound of Claim 7 wherein R¹ and R² together with the carbon atom to which
2 they are attached form tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-
3 dioxohexahydrothiopyran-4-yl.

1 11. A compound selected from the group consisting of:
2 *N*-(1-cyanocyclopropyl)-3-(4-trifluoromethylpyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-
3 trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
4 *N*-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
5 fluorophenylethylamino)propionamide;
6 *N*-(1-cyanocyclopropyl)-3-pyridan-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
7 fluorophenylethylamino)propionamide;
8 *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylfuran-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-
9 trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
10 *N*-(1-cyanocyclopropyl)-3-pyrimidin-5-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
11 fluorophenylethylamino)propionamide;
12 *N*-(1-cyanocyclopropyl)-3-(2-methylthiazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-
13 4-fluorophenylethylamino)propionamide;
14 *N*-(1-cyanocyclopropyl)-3-pyridin-4-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
15 fluorophenylethylamino)propionamide;
16 *N*-(1-cyanocyclopropyl)-3-pyrimidin-4-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
17 fluorophenylethylamino)propionamide;
18 *N*-(1-cyanocyclopropyl)-3-[2-(1-oxopyrrol-1-yl)ethanesulfonyl]-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
19 fluorophenylethylamino)propionamide;
20 *N*-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*R*)-4-
21 fluorophenylethylamino)propionamide;
22 *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-3-
23 fluorophenylethylamino)propionamide;
24 *N*-(1-cyanocyclopropyl)-3-(3,3,3-trifluoropropane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
25 fluorophenylethylamino)propionamide;

- 26 *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylpyridin-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-
27 trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- 28 *N*-(1-cyanocyclopropyl)-3-(4-[1,2,4]-triazol-1-ylphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-
29 1(*S*)-4-fluorophenylethylamino)-propionamide;
- 30 *N*-(1-cyanocyclopropyl)-3-[2-(2-oxo-2,3-dihydrobenzimidazol-1-yl)ethanesulfonyl]-2(*R*)-
31 (2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- 32 *N*-(1-cyanocyclopropyl)-3-(5-oxo-pyrrolidin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-
33 4-fluorophenyl-ethylaminopropionamide;
- 34 *N*-(1-cyanocyclopropyl)-3-(2-fluoropyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-
35 4-fluorophenyl-ethylaminopropionamide;
- 36 *N*-(1-cyanocyclopropyl)-3-(3-methyloxetan-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-
37 4-fluorophenylethylamino)propionamide;
- 38 *N*-(1-cyanocyclopropyl)-3-(2-phenylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
39 fluorophenylethylamino)propionamide;
- 40 *N*-(1-cyanocyclopropyl)-3-(3,3,3-trifluoropropane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-4-
41 fluorophenylethylamino)propionamide;
- 42 *N*-(1-cyanocyclopropyl)-3-(fluoropyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
43 fluorophenylethylamino)propionamide;
- 44 *N*-(1-cyanocyclopropyl)-3-(fluoropyrazin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
45 fluorophenylethylamino)propionamide;
- 46 *N*-(1-cyanocyclopropyl)-3-(difluoropyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
47 fluorophenylethylamino)propionamide;
- 48 *N*-(1-cyanocyclopropyl)-3-(difluoropyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
49 fluorophenylethylamino)propionamide;
- 50 *N*-(1-cyanocyclopropyl)-3-(quinolin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
51 fluorophenylethylamino)propionamide;
- 52 *N*-(1-cyanocyclopropyl)-3-(benzo[1,2,5]thiadiazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-
53 1(*S*)-4-fluorophenyl-ethylamino)propionamide;
- 54 *N*-(1-cyanocyclopropyl)-3-(benzothiazol-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
55 fluorophenylethylamino)propionamide;
- 56 *N*-(1-cyanocyclopropyl)-3-(5-methylisoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-
57 4-fluorophenyl-ethylamino)propionamide;
- 58 *N*-(1-cyanocyclopropyl)-3-(2-methylpropylsulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
59 fluorophenylethylamino)propionamide;

- 60 *N*-(1-cyanocyclopropyl)-3-(cyclobutylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
61 fluorophenylethylamino)propionamide;
- 62 *N*-(1-cyanocyclopropyl)-3-(2,6-difluorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
63 fluorophenylethylamino)propionamide;
- 64 *N*-(1-cyanocyclopropyl)-3-(2,4-difluorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
65 fluorophenylethylamino)propionamide;
- 66 *N*-(1-cyanocyclopropyl)-3-(quinolin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
67 fluorophenylethylamino)propionamide;
- 68 *N*-(1-cyanocyclopropyl)-3-(4,4,4-trifluorobutyl-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
69 fluorophenylethylamino)propionamide;
- 70 *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-
71 1(*S*)-4-fluorophenylethylamino)-propionamide;
- 72 *N*-(1-cyanocyclopropyl)-3-(2-trifluoromethoxyphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-
73 1(*S*)-4-fluorophenylethylamino)-propionamide;
- 74 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,5-
75 difluorophenylethylamino)propionamide;
- 76 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,5-
77 difluorophenylethylamino)propionamide;
- 78 *N*-(1-cyanocyclopropyl)-3-(2-pyridin-2-ylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
79 fluorophenyl-ethylamino)propionamide;
- 80 *N*-(1-cyanocyclopropyl)-3-(2-pyridin-3-ylethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
81 fluorophenyl-ethylamino)propionamide;
- 82 *N*-(1-cyanocyclopropyl)-3-(quinolin-8-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
83 fluorophenyl-ethylamino)propionamide;
- 84 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,3-
85 difluorophenylethylamino)propionamide;
- 86 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,4-
87 difluorophenylethylamino)propionamide;
- 88 *N*-(1-cyanocyclopropyl)-3-(5-methyl-3-phenylisoxazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-
89 trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- 90 *N*-(1-cyanocyclopropyl)-3-(4-methyl-2-phenyl-[1.2.3]triazol-5-ylmethanesulfonyl)-2(*R*)-
91 (2,2,2-trifluoro-1(*S*)-4-fluorophenyl-ethylamino)-propionamide;
- 92 *N*-(1-cyanocyclopropyl)-3-(2-cyanophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
93 fluorophenyl-ethylamino)propionamide;

- 94 *N*-(1-cyanocyclopropyl)-3-(3-methoxycarbonylphenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-
95 1(*S*)-4-fluorophenylethylamino)-propionamide;
- 96 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2-difluoro-1(*S*)-4-
97 fluorophenyl-ethylamino)propionamide;
- 98 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*RS*)-2-
99 chloropyridin-5-ylethylamino)propionamide;
- 100 *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-
101 fluorophenylpropylamino)propionamide;
- 102 *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-
103 1(*S*)-4-fluorophenylpropylamino)-propionamide;
- 104 *N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-
105 fluorophenylpropylamino)propionamide;
- 106 *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-
107 1(*S*)-4-fluorophenylpropylamino)-propionamide;
- 108 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-
109 fluorophenylpropylamino)propionamide;
- 110 *N*-(1-cyanocyclopropyl)-3-(quinoxalin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
111 fluorophenylethylamino)propionamide;
- 112 *N*-(1-cyanocyclopropyl)-3-(tetrahydropyran-2*RS*-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-
113 1(*S*)-4-fluorophenylethylamino)-propionamide;
- 114 *N*-(1-cyanocyclopropyl)-3-(2,6-dichlorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
115 fluorophenylethylamino)propionamide;
- 116 *N*-(1-cyanocyclopropyl)-3-(3-methoxycarbonylfuran-2*RS*-ylmethanesulfonyl)-2(*R*)-(2,2,2-
117 trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide;
- 118 *N*-(1-cyanocyclopropyl)-3-(5-methylisoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-
119 pentafluoro-1(*S*)-4-fluorophenylpropylamino)-propionamide;
- 120 *N*-(1-cyanocyclopropyl)-3-(2,2-dimethylpropylsulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
121 fluorophenylethylamino)propionamide;
- 122 *N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*R*)-4-
123 fluorophenylpropylamino)propionamide;
- 124 *N*-(1-cyanocyclopropyl)-3-(ethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
125 fluorophenylethylamino)propionamide;
- 126 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,5-
127 difluorophenylethylamino)propionamide;

- 128 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,6-
129 difluorophenylethylamino)propionamide;
- 130 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,6-
131 difluorophenylethylamino)propionamide;
- 132 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,3-
133 difluorophenylethylamino)propionamide;
- 134 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,4-
135 difluorophenylethylamino)propionamide;
- 136 *N*-(1-cyanocyclopropyl)-3-(methanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
137 fluorophenylethylamino)propionamide;
- 138 *N*-(1-cyanocyclopropyl)-3-(propane-1-sulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
139 fluorophenylethylamino)propionamide;
- 140 *N*-(1-cyanocyclopropyl)-3-(1*H*-indol-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
141 fluorophenylethylamino)propionamide;
- 142 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-
143 fluorophenylethylamino)propionamide;
- 144 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-
145 fluorophenylethylamino)propionamide;
- 146 *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,4-
147 difluorophenylethylamino)propionamide;
- 148 *N*-(1-cyanocyclopropyl)-3-(pyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-3,4-
149 difluorophenylethylamino)propionamide;
- 150 *N*-(1-cyanocyclopropyl)-3-[2-(1*H*-indol-3-yl)ethanesulfonyl]-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
151 fluorophenylethylamino)propionamide;
- 152 *N*-(1-cyanocyclopropyl)-3-(tetrahydropyran-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-
153 4-fluorophenylethylamino)propionamide;
- 154 *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-
155 fluorophenylethylamino)propionamide;
- 156 *N*-(1-cyanocyclopropyl)-3-(1-oxopyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-
157 fluorophenylethylamino)propionamide;
- 158 *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-
159 fluorophenylethylamino)propionamide;
- 160 *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2-
161 fluorophenylethylamino)propionamide;

162 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2,3,4-
 163 trifluorophenylethylamino)propionamide;
 164 *N*-(1-cyanocyclopropyl)-3-(cyclopropylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*R*)-2,3,4-
 165 trifluorophenylethylamino)propionamide;
 166 *N*-(1-cyanocyclopropyl)-3-(2,2,2-trifluoroethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-
 167 fluorophenylethylamino)propionamide;
 168 *N*-(1-cyanocyclopropyl)-3-(benzoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-2-
 169 fluorophenylethylamino)propionamide;
 170 *N*-(1-cyano-cyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(3-
 171 hydroxy-6-methyl-pyridin-2-yl)-ethylamino]-propionamide;
 172 *N*-(1-cyanocyclopropyl)-3-(2-*tert*-butyl-[1.3.4]-thiadiazol-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-
 173 trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;
 174 *N*-(1-cyanocyclopropyl)-3-(2,4,6-trifluorophenylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-
 175 4-fluorophenylethylamino)propionamide;
 176 *N*-(1-cyanocyclopropyl)-3-(2-pyridin-2-ylethanesulfonyl)-2(*R*)-(2,2,3,3,3-pentafluoro-1(*S*)-4-
 177 fluorophenylpropylamino)propionamide;
 178 *N*-(1-cyanocyclopropyl)-3-(1-ethyl-2,5-dioxopyrrolidin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-
 179 trifluoro-1(*S*)-4-fluorophenyl-ethylamino)propionamide; and
 180 *N*-(1-cyanocyclopropyl)-3-(benzoxazol-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-
 181 fluorophenylethylamino)propionamide or
 182 a pharmaceutically acceptable salt thereof.

1 12. A pharmaceutical composition comprising a compound of any of the Claims 1-11 in
 2 admixture with one or more suitable excipients.

1 13. A method for treating a disease in an animal mediated by Cathepsin S which method
 2 comprises administering to the animal a pharmaceutical composition comprising a compound
 3 of any of the Claims 1-11 in admixture with one or more suitable excipients.

1 14. The method of Claim 12 wherein the disease is rheumatoid arthritis, multiple
 2 sclerosis, myasthenia gravis, psoriasis, pemphigus vulgaris, Graves' disease, myasthenia
 3 gravis, systemic lupus erythematosus, asthma, pain, and atherosclerosis.

1 15. A method of treating a patient undergoing a therapy wherein the therapy causes an
 2 immune response in the patient comprising administering to the patient a compound of any of
 3 Claims 1-11.

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